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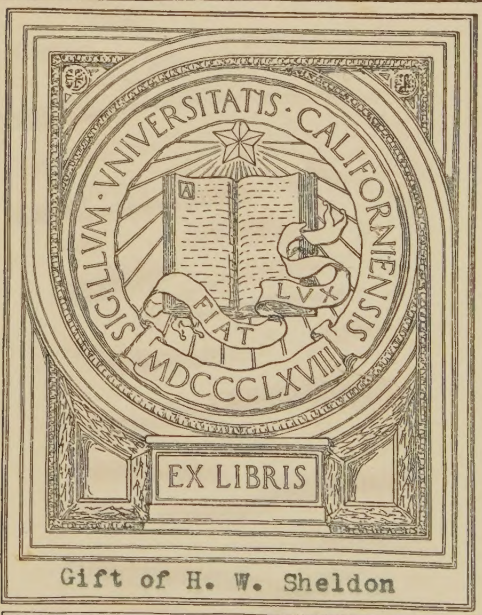

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The

Practical Medicine Series

COMPRISING EIGHT VOLUMES ON THE YEAR'S PROGRESS IN MEDICINE AND SURGERY

Under the General Editorial Charge of

CHARLES L. MIX, A.M., M.D.

Volume VI

General Therapeutics

EDITED BY

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PREFACE

The Editor's aim is to let practical value rather than news value determine admission to these pages on "General Therapeutics." As long as, for example, insulin and intarvin were merely news items and very little was definitely known regarding their utility, it seemed best not to burden the reader with possibly untrustworthy accounts. Now it seems evident that intarvin is of but little value in the treatment of diabetes while insulin is one of the great outstanding discoveries of the age; and proportionate space has been allotted to these items.

Though barely two years have elapsed since Banting announced his discovery, literally many hundreds of articles and several books on it have appeared in print. It is obvious that but a limited number of these could be abstracted here. Though a conscientious and careful selection has been made of those to be included, still the insulin section has become the largest in this volume.

Among the newer remedies discussed might be mentioned: mercurochrome, sulpharsphenamin, tryparsamid, hexylresorcinol, carbon tetrachlorid, carbon dioxid-oxygen, novasurol, ethylene, tutocain, scillaren. On the other hand, irradiated oils, "sanochrysin" and certain other new agents not yet available for general use, opinion regarding the value of which has not yet crystallized, it was thought best to omit.

Osmotherapy and non-specific tissue stimulation looms large among the newer and unusual ways of administration of old and common agents for therapeutic purposes. The term "non-specific proteotherapy" previously applied to the latter mode of treatment is no longer correct, as such substances as distilled water, alcohol, sulphur and colloidal metals have been shown to produce the same kind of effect.

BERNARD FANTUS.

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GENERAL THERAPEUTICS

Real and Supposed Results in Treatment. George Edward Barnes[1] would like to have the common statement, "Results are what talk," changed to "What people think are results is what talks." People patronize a thing not so much according to its real worth as according to what they think it is worth. There is little doubt that people in general more often form an erroneous than a correct idea about the results of treatment of diseases. Real logical, scientific, constructive thinking is hard; careless assumption is easy.

Improvement following any kind of treatment may wrongly be considered to be the result of that treatment in three chief, particular ways.

1. Through some change caused by nature not connected with the treatment—the natural course of events, usually nature's own reparative processes, improvement may result. As a matter of fact, most diseases tend to improve or be cured without any treatment, and when some form of treatment has been given in such cases and improvement or restoration to health has taken place, it is very easy to say that the improvement is due to the "treatment" instead of to the natural recuperative powers of human tissues.

2. Improvement may follow some suggestion given to people who are more or less sick on account of affective or emotional disturbances. The most frequent mental activities of this sort have to do with great concern about a matter of love, business or health. When a person in this condition receives any kind of treatment whatsoever, even a kind word or a slap on the back, he may feel better simply because the idea of the thing that is bothering him is replaced more or less by the idea of the treatment or other thing, and the disturbing affective currents therefore become altered.

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(1) Amer. Med., October, 1924.

3. There are people who are sick and who, on account of their excessive suggestibility and credulity, believe that they are improving or that they are already cured when they are still sick and not improving, or are getting worse and are even near death.

These three ways in which unscientific forms of treating disease may wrongly be given credit for improvement or cure should be thought of in relation to any form of treatment whose distinctive claims are being studied, and if any form of treatment cannot show real scientific results in addition to the false "results" arising in these three ways, it can possess no intrinsic scientific value. The difference between treatment by a learned doctor of medicine and treatment by other "practitioners," is that the latter produce only so-called "results" in the three above-mentioned casual ways, whereas medical men with good knowledge endeavor to make a scientific diagnosis and to produce, in addition to the casual "results," all possible beneficial, actually scientific results, giving the patient that treatment which his individual condition requires.

Legislators should realize, that in permitting the existence of any form of quackery on the claim that it does no harm and may sometimes do some good, they are making two big errors: they are hindering the progress of true medical science and they are not protecting the people from injurious humbugs.

GENERAL THERAPEUTIC TECHNIC

INCOMPATIBILITIES

Incompatibilities. Percy May[2] reviews a number of incompatibilities of drugs of which it might not be amiss to be reminded.

Saccharin is a substance, the strongly acid nature of which is often unrecognized. It is one of the strongest organic acids. In cases where its acidity may be unde-

(2) Lancet, Mar. 29, 1924.

sirable, its stable and soluble sodium or ammonium salt (soluble saccharin) may advantageously be used instead. There are also some substances that are neutral when quite pure, but which readily give acid decomposition products when in solution or in the presence of moisture. Spirit of nitrous ether and solution of ethyl nitrite are good examples of this type, and for this reason it may be advisable to neutralize the spirit with potassium bicarbonate before using it in mixtures where the presence of acid may be a disturbing factor. Among the substances which it is inadvisable to prescribe with compounds of acid reaction are ammonium acetate, tartar emetic, all nitrites, and the soluble salts of salicylic and benzoic acids.

The alkaline nature of sodium and potassium salts of weak acids, such as the carbonates, is well recognized; but it should be noted that borax is also strongly alkaline, and on this account is incompatible with many substances. Thus, for example, solutions of borax are sufficiently alkaline to absorb carbon dioxid with formation of sodium bicarbonate and boric acid, and when warm their alkalinity is even great enough to decompose chloral with formation of chloroform and sodium formate. Solutions of borax also precipitate alkaloids from solutions of their salts. Borax precipitates insoluble borates of nearly all the matals from solutions of their salts, though these precipitates are sometimes soluble in excess of borax or in solutions of ammonium salts. The presence of glycerin often prevents this precipitation. Borax and hydrogen peroxid is unstable in alkaline solution, and the pressure of oxygen evolved from it may burst the container. On the other hand, the alkalinity of borax accounts for many of its valuable properties, such as its power of dissolving casein, fibrin, uric acid, and many resins, and of forming stable emulsions with many oils, often superior to those obtained with lime. One striking peculiarity of borax is the fact that it develops an acid reaction in the presence of glycerin, and is then incompatible with carbonates, from which it lib-

erates carbon dioxid. Glucose, honey and other polyhydroxy-alcohols share this peculiarity with glycerin. Another incompatibility of borax is that it forms a moist mass when triturated with alum, through liberation of the water of crystallization of the latter.

Sodium and potassium compounds of weak acids are sometimes strongly alkaline; and veronal-sodium, for example, is sufficiently alkaline to cause evolution of ammonia when prescribed with ammonium bromid. Potassium bromid should, of course, be used instead in this case. Soaps, also, have an alkaline reaction, and this should be remembered in connection with soap emulsions and liniments. Many substances which are neutral when pure may be alkaline in the ordinary specimens met with in practice. For example, ordinary commercial sodium cacodylate is usually alkaline though it is neutral when quite pure.

It stands to reason that an oxidising agent will be incompatible with a reducing agent, but a more remarkable incompatibility sometimes met with is that of two oxidising agents together, which reduce each other with liberation of free oxygen. Hydrogen peroxid and potassium permanganate are a pair of this type. They are reduced to water and manganese dioxid with evolution of oxygen, and therefore should not be prescribed together. Chloramine-T is another antiseptic oxidising agent to which this applies, as it reduces hydrogen peroxid with evolution of oxygen. Hydrogen peroxid is also reduced by alcohol, and is reduced catalytically by many other substances, among which organic silver compounds are noteworthy.

Hexamethylenamin is noteworthy among the substances which have many incompatibilities, and caution should always be used in prescribing it with other substances.

Bromids and iodids are dangerous with calomel, particularly in the presence of oxidising agents; and free

iodin or its preparations should be most carefully avoided when calomel is being administered.

Physical incompatibility, due to the influence of one dissolved substance in lowering the solubility of another, whereby the latter is thrown out of solution is sometimes overlooked. When one of the substances is of a saline nature, the phenomenon is often known as "salting out." In this way codein bromid is salted out by an excess of sodium bromid, and very many other instances of this type are to be met with. As most salts are less soluble in dilute alcohol than in water, the presence of alcohol in any form is liable to cause crystallization of sparingly soluble salts. Potassium chlorate, for example, crystallizes out very readily in the presence of alcohol.

In powder mixtures trouble may be caused by the mutual lowering of the melting-point of the components of a mixture. It is well known that an impure substance has a lower melting-point than when in a pure state, and therefore it is not very surprising to find that where two substances of moderately low melting-point are mixed, the melting-point of the mixture may be low enough for it to be liquid at ordinary temperatures. For example, salol (melting-point 43° C.) gives with antipyrin (melting point 114° C.) a mixture of melting-point at 30° C., with menthol one melting at 28° C., with chloral hydrate, one melting at 17° C., with camphor (melting point 175° C.), one melting at 6° C., and with guaiacol one melting at 3° C., the first two of these may liquify in hot weather and the others will be liquid at all ordinary temperatures.

Many interesting cases have been recorded of undesirable effects being produced by one drug reacting through the body fluids with another drug taken previously, or by a drug taken internally reacting with another taken externally. For example, mercury oxycyanid is a non-irritant and valuable medium for bladder and urethra irrigation, but in patients under the influence of iodids it causes intense cystitis through formation of ir-

ritant mercuric iodid. A case has been observed of severe burning of the skin on the application of hydrogen peroxid lotion to a patient undergoing internal treatment with potassium iodid through the liberation of free iodin. On account of the irritant nature of mercuric iodid, dressings of corrosive sublimate should not be used on wounds previously treated with tincture of iodin. If this should happen, the mercuric iodid is best removed by washing with potassium iodid solution. A similar incompatibility is recorded in the use of external applications of mercury and the internal use of sulphur compounds, brown or black stains of mercuric sulphid having been produced on the skin.

Incompatibles of Barbital Derivatives. W. Zimmermann[3] calls attention to the fact that barbital and phenobarbital are such feeble acids that their sodium salts are readily dissociated by the feeblest acids. Thus such solutions would be precipitated by fruit juices containing organic acids such as citric acid.

The dissociation of the sodium salt in aqueous solutions produces enough O H ions to liberate ammonia from ammonium salts and to precipitate alkaloids, such as morphin and quinin, from aqueous solutions of their salts.

ADMINISTRATION OF DRUGS

In General

The Time at Which to Take Drugs. The Practitioner of January, 1924, abstracts from Lemoine[4] rules which should be more generally known. All prescriptions in which quickness of action is desired should be taken before meals. A hypnotic will promote sleep much more quickly if taken before supper than if it is swallowed before going to bed. It will act equally well in a small dose, for, if given after supper, instead of

(3) Pharmaz. Zentralh., Apr. 24, 1924.
(4) Jour. de Therapeutique Franc., October, 1923.

being absorbed *en masse,* it will be slowly ingested from the midst of a bolus of food.

Drugs of which the action is slowly shown should be given at the end of a meal, which in most cases will allow a stomach full of food to tolerate them better than when empty. This includes all therapeutic agents, the action of which is "long dated." The same thing applies to drugs with a disagreeable flavor.

Some drugs must be given at a time determined by relation to meals. Bitters should be taken at least half an hour to an hour before the meal. Alkalies, most absorbing powders, and belladonna should only be given at the moment when the gastric pains, like those of hyperacidity, show themselves, that is to say, about two hours after meals, at the time when digestion is stopped and the pains appear from the fact of the renewed acidity.

The action of quinin shows itself about seven hours after its ingestion, which is the guide for its administration in malaria. Hypothermic drugs should be taken at a certain time before the appearance of the rise of temperature, so as to check its rise rather than to reduce it when it has risen and wearied the patient. Purgatives should be taken in the morning fasting, with the precaution of not eating for an hour later and very sparingly. On the other hand, laxatives should be taken at night two hours after the meal, so as to act in the morning. An injection of arsenobenzol should not be given after a meal. Breaking this rule has caused accidents. Enemata should be given before and not after a meal.

Duodenal Tube

Duodenal Tube Drainage and Lavage. W. L. Brown and C. P. Brown[5] believe that the duodenal tube is still not being used to the extent it merits. They consider it one of the most important adjuncts to diagnosis and treatment in both medical and surgical cases invented in recent years.

(5) Jour. Amer. Med. Ass'n., Aug. 9, 1924.

Experimental work having shown the duodenum and upper jejunum to be the toxic zone in intestional obstructions, whether adynamic or mechanical in nature, duodenal tube drainage suggests itself as a simple and important therapeutic measure in such cases.

In the majority of cases the authors have used the Jutte tube with a small metallic tip or sinker. For the first two years they passed it through the mouth. More recently they have been passing it through the nose, and find this a much more satisfactory method. When it is passed through the mouth of seriously ill surgical patients, who are vomiting, it is usually necessary to insert a wire to bring about sufficient stiffness for its passage. Many of the patients have been unable to swallow the tube voluntarily. When it is passed through the nose, however, they nearly all swallow it without difficulty, if allowed to drink water.

The Levin (1921) gastroduodenal catheter for passage through the nose has some advantages over the Jutte tube because of additional stiffness. They prefer the glass syringe with a rubber bulb for emptying the stomach and lavage because it can be manipulated with the right hand and the left hand used for connecting and disconnecting the tube. This also has an advantage over the piston syringe, in that there is no plunger to be constantly out of order.

The tube used has several advantages over the stomach tube. 1. It is much smaller and less disagreeable to use. 2. It empties the stomach positively by suction instead of uncertainty by siphonage. 3. It may be used for lavage or left for continuous drain and lavage, from a few hours to several days, according to the indications. If continuous drainage is not desirable, when it is thought the patient will absorb the water, or following medication given through the tube, it may be snapped with a light hemostat. 4. The patient can drink water freely while the tube is in place. 5. Certain patients can have transgastric fluids and feeding when they are

greatly dehydrated and debilitated because of a prolonged illness prior to operation.

The tube should be used before operation in all cases of prolonged vomiting from gastric ulcer, pyloric obstruction, marasmus from prolonged starvation, and other cases in which there are indications for the administration of fluids and nourishment.

Patients who have vomited practically all fluids taken for weeks may be given transgastrically fluid and nourishment until they are relieved of dehydration and acidosis. In cases of acute intestinal obstruction the authors use the tube for lavage before the operation and leave it in place during and after the operation if it has been passed through the nose.

The tube should be used after operation: (1) in all cases of prolonged vomiting, distention and thirst, whatever the cause; (2) in cases of peritonitis, post-operative intestinal obstruction, resections, gun-shot wounds and gallbladder operations.

It is an invaluable adjunct in relieving gas pressure on the line of suture and in instituting drainage in operations on the stomach for ulcers, following resection or gastroenterostomy, when the patients are inclined to vomit too much and have distention or dilatation.

Intravenous Medication

Objections to Indiscriminate Use of Intravenous Medication. Hanzlik[6] concludes a paper on "Allergic Phenomena" with the following practical considerations. Used intravenously, such common agents as hexamethylenamin, iodid and salicylate cause definite chemical and physical changes in the blood of animals, disturbing and injurious to important functions and tissues. There is no justification for the intravenous administration of such agents as hexamethylenamin, sodium iodid and sodium salicytate, because their ordinary systemic effects are readily and promptly obtained from oral ad-

(6) Jour. Amer. Med. Ass'n., June 21, 1924.

ministration. On the contrary, other and more detrimental effects may be obtained from intravenous administration.

An agent injected intravenously may be temporarily beneficial to one function, but detrimental to others and to the organisms as a whole. This is illustrated by the intravenous use of acacia in shock and similar conditions. By the use of acacia, a single function may be raised and maintained at a high level for a time. However, the net result for the organism is no better, and is usually worse than by other methods of treatment, injurious effects in and greater mortality of animals, than from other solutions having been demonstrated and also severe reactions and death in patients. Even isotonic sodium chlorid solution is not physiologic, but is not as injurious as some other agents and solutions.

The intravenous effects of agents cannot be predicted from their physical and chemical properties, and from their physiologic effects when given by mouth. For instance, agar, which is chemically inert and harmless when given by mouth, produces violent reactions and even death when injected intravenously in minute doses. From all this it follows that the indiscriminate and careless use of drugs by intravenous injection is irrational, unscientific and dangerous.

Sodium and Not Potassium Salts Should Be Administered Intravenously. David Loeser and A. Lincoln Konwiser[7] show by injections in young white rats that potassium salts are far more toxic intravenously than the corresponding sodium salts. Therefore, when the effect of iodid or other acid radical is desired, the sodium rather than the potassium salts should be used intravenously.

[That this is so has been known for a long time.—Ed.]

Inhalation

Blotting Paper Inhaler. Ludwig Darmstaedter[8] recommends the following very simple method in

(7) Jour. Lab. and Clin. Med., March, 1924.
(8) Klin. Wochenschr., May 13, 1924.

lieu of complicated and expensive inhalers. A small piece of absorbing paper, such as filter paper or blotting paper, with three to four drops of volatile fluid completes the inhalation apparatus. The paper is held about two inches from the nose or mouth; if the nose is affected, the patient breathes with the mouth closed. It usually suffices to take 20 to 25 breaths a minute for three or four minutes. The inhalations should be practiced at least four times daily. The author recommends purified oil of turpentine as one of the best inhalants in acute as well as in chronic catarrh.

Intratracheal Injection

Intratracheal Injection of Oils. On the basis of an experience with 160 selected cases of tuberculous laryngitis in the past fifteen months treated with intratracheal injections of chaulmoogra oil, James E. Lebensohn[9] finds that this method of treatment is most efficacious in those patients whose laryngeal lesions were incipient or only moderately extensive. He also believes that intratracheal injection of oils is a valuable therapeutic measure for many other conditions in the upper respiratory tract. In all of of them an oily base is necessary, as this is well tolerated by the larynx, while a watery solution injected intratracheally produces laryngospasm and strangling cough.

Oil injections have been found of value in most inflammatory conditions of the larynx, trachea, and bronchi. The irritating cough is very favorably affected. There is no clinical evidence that such injections judiciously employed, cause any constitutional disturbance either immediate or remote. They aid in providing the desired rest of the crico-arytenoid joints, and true and false vocal cords which furthers a cure. By coating the surface of the laryngeal mucous membrane, adherent oily antiseptics tend to prevent fresh tubercular (or other) infection of the mucous glands and the slight

(9) Ill. Med. Jour., November, 1923.

epithelial abrasions caused by coughing. Finally, they are of use in inhibiting the secondary surface sepsis which aggravates and encourages the advance of infection.

The unfavorable reactions and deaths obtained from intratracheal injections by Corper and Freed merely prove the extreme susceptibility of the rabbit to the intratracheal injection of oils in tremendous contrast to the tolerance of man.

Lumbar Puncture

Small Needle for Lumbar Puncture. C. S. Bluemel[1] describes a very small needle shown in accompanying illustration (three to three and one-half inch No. 24 gage), for making spinal punctures. The sliding sleeve serves as a "holder" and prevents the bending and wobbling that would otherwise occur in performing lumbar puncture with a small caliber needle. The obturator is made of No. 0 cast steel music wire. The needle must be exquisitely sharp in order that it may puncture the dura cleanly instead of tearing the dura and leaving in it a hole larger than itself. (Fig. 1.)

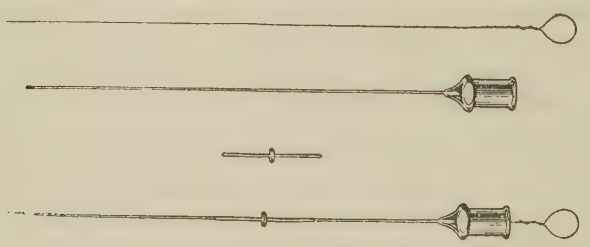


Fig. 1.—Needle used for lumbar puncture: the sliding sleeve serves as a holder and prevents bending.

The small needle is employed to reduce the size of the puncture-hole in the dura, and thus diminish the subsequent escape of spinal fluid into the tissues. Marked decrease in the incidence of postpuncture headache results.

(1) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

Before the lumbar puncture is performed, the obturator wire is withdrawn a short distance into the needle. When the spinal canal has been penetrated, the obturator can be pushed forward through the point of the needle. The obturator is then withdrawn and the spinal fluid normally flows at a rate of from sixteen to twenty-four drops a minute with the patient in the sitting position.

The patients are required to lie flat on the back for half an hour after the puncture, and are then allowed to resume their accustomed activities. These needles are manufactured by Becton, Dickinson & Co., Rutherford, N. J.

TECHNICISMS

For Sterilization of Rubber Gloves. Lothar am Ende[2] recommends a sodium hypochlorite solution in concentration of 0.382 per cent. for one hour.

T. Schultz[3] recommends boiling rubber gloves for twenty minutes in strong salt solution (12½ per cent.) in a covered vessel. Gloves keep soft and elastic, and do not stretch.

Dental Cement for the Removal of Foreign Bodies in the Ear. O. Jansen Dixon[4] recommends dental cement mixed in the usual manner, a small lump of which, when fairly thick, is inserted by means of a camel's hair brush into the ear canal and held firmly against the foreign body for a couple of minutes, and then withdrawn. It is surprising how firmly the cement holds to the foreign body as it passes through the external auditory meatus.

Pancreatin Dressing for Ulcers. For the cleansing of wounds containing necrotic material, K. E. Hirsch-

(2) Münch. med. Woch., June 20, 1924.
(3) Ugeskrift for Læger, May 8, 1924.
(4) Jour. Amer. Med. Ass'n., Aug. 2, 1924.

feld[5] recommends the use of the following powder or ointment:

Pancreatin	2 gm.
Zinc oxid	15 gm.
Talcum	83 gm.

In the ointment, petrolatum is used instead of the same amount of talcum. The powder is to be preferred to the ointment in wounds with more profuse secretions.

He finds this treatment useful in vericose ulcers, bed sores, suppurating wounds and burns, as well as in furuncles and carbuncles. In the treatment of the latter it is often possible to accelerate healing by removing the pointing top and covering the infiltrated field with pancreatin salve. After crucial incision of large carbuncles of the neck the pancreatin powder is especially useful. These preparations are so efficient that it gives one the impression that diseased and dying tissue is literally eaten away and digested by the preparation.

(5) Klin. Wochenschr., July 15, 1924.

ETIOTROPIC THERAPY

IN GENERAL

Limitations of Antiseptics. Marsh Pitzman[6] concludes that confusion results from the failure to draw a sharp distinction between the prophylaxis of infections and the treatment of infection. The power of germicides as prophylactics against subsequent infection is almost unanimously accepted in regard to the conjunctiva, less firmly established in regard to the urethra, and distinctly doubtful in regard to traumatic wounds through the skin. Except by preventing secondary infections of already infected wounds, antiseptics and germicides have ordinarily no influence on the course of a surgical infection. It is scientifically doubtful as to whether antiseptics or germicides are an indispensable element in the proper treatment of established infections of the mucous membranes.

THE HALOGENS

Chlorin

Chlorin Inhalation. Austin O'Malley[7] calls attention to the fact that chlorin was used in respiratory infections as early as 1833, as shown by a note in "The Transactions Médicales" for February, 1833, by Dr. Bourgeois.

This physician, having seen two apparently desperate phthisical patients relieved without being submitted to any medical treatment, but who resided at a bleaching establishment near St. Denis, the atmosphere of which is impregnated with chlorin, was induced to form a similar atmosphere in the chambers of some phthisical patients in the Royal School at St. Denis. This medication, though it did not cure these patients, ameliorated

(6) Jour. of the Missouri State Med. Ass'n., November, 1923.
(7) Jour. Amer. Med. Ass'n., Aug. 2, 1924.

their condition, diminished their dyspnea, promoted sleep, gave them appetite, and destroyed the fetor of their sputa.

Harry L. Gilchrist[8] states that chlorin was used therapeutically even earlier than this, that one hundred years ago, in 1824, William Wallace of Dublin used chlorin and recommended a trial of it on general principles in every disease of whatever kind it may be, which we might naturally hope to benefit by stimulating or restoring the functions of the skin, or by keeping up in this important covering a state of permanent irritation.

The origin of the present apparently successful use of chlorin for the treatment of respiratory disease dates back to 1918 and had its genesis in the observations of medical officers in our Army who were stationed along the front lines. There it was observed that, notwithstanding that the great influenza epidemic was filling the hospitals with those stricken with the disease, the hospitals in the front areas were almost devoid of cases of this nature. Consequently, it did not take the medical officers long to attribute this immunity in the trenches to the presence of gas. They not only took advantage of the immunizing effects of chlorin, but used it for treatment.

Edward B. Vedder and Harold P. Sawyer[9] determined to investigate the value of chlorin as a therapeutic agent, as it had been observed that during the war, when the chlorin plant at Edgewood Arsenal was producing to full capacity, and the great influenza epidemic struck the post, filling the hospital to overflowing, it was stated that no cases were recorded among the operatives of the chlorin plant, although every other organization on the arsenal had its full quota of cases.

To determine the concentration of chlorin in air required to kill bacteria, they exposed agar plates inocu-

(8) Wisconsin Med. Jour., October, 1924.
(9) Jour. Amer. Med. Ass'n., Mar. 8, 1924.

lated with the organism to be tested to a known concentration of chlorin. These experiments showed that the different bacteria used were all killed by concentration of 0.021 mgm. of chlorin per liter, if the time of exposure was sufficient; also that the more delicate organisms, such as the meningococcus and M. Catarrhalis, were killed after an hour's exposure to this concentration. There is good reason to believe that the organisms producing the common cold and influenza belong to the group of so-called filtrable viruses, and may be even more susceptible to the action of chlorin than are ordinary bacteria. They also found that the concentration of 0.021 mgm. per liter, which killed bacteria, is well within the limit of safety.

The effect of inhaling chlorin on the bacteria of the nasopharynx was then tested on about 50 cases with practically uniform results. A treatment of half an hour did not diminish the growth in the second culture; 45 minute exposures reduced the colony count to about half, while hour exposures appeared practically sufficient to sterilize the tonsillar, postnasal and pharyngeal surfaces. In therapeutic work, a concentration of approximately 0.015 mgm. of chlorin per liter was used, as some persons found that 0.02 caused slight irritation of the throat.

The cases treated and results obtained are shown in Table 1. Most of the patients received a single treatment of one hour. A few received a second or even a third treatment on succeeding days. The results obtained were very gratifying. There seems to be little doubt that such chlorin treatment will completely abort a cold when taken sufficiently early, and in well developed cases it affords great relief. Acute bronchitis is practically always relieved. There is more difficulty in treating "head colds" because the swelling of the mucous membrane stops the air passages and prevents free access to the chlorin. In a number of later cases, the nose was first treated with epinephrin in order to shrink the mucous membranes and obviate this difficulty.

The authors also believe that this treatment may be used to free meningococcus carriers of their organisms, and that such a sterilizing treatment might be of value prior to operations on the nose and throat. They describe a portable apparatus developed for this purpose by the Wallace and Tiernan Company, of New York.

TABLE 1.—*Total Cases Treated; Number of Cured, Improved and Unimproved, with Percentage for Each*

Diagnosis	No. of Cases	Cured		Improved		No Chge.	
		No.	%	No.	%	No.	%
Coryza	388	288	74.2	91	23.5	9	2.3
Acute laryngitis and pharyngitis	127	99	78.0	24	19.0	4	3.1
Acute bronchitis	241	192	80.0	47	19.5	2	0.5
Chronic rhinitis	106	33	31.1	41	38.6	32	30.2
Chronic bronchitis	47	34	72.3	12	25.5	1	2.1
Chronic laryngitis	2	2	100.0	..	...	..	...
Whooping cough	9	8	88.8	1	11.1	..	...
Influenza	11	9	81.8	2	18.1	..	...
	931	665	71.4	218	23.4	48	5.1

The success of the treatment depends largely upon the introduction of a sufficient amount of chlorin gas for a sufficient length of time.

Harry L. Gilchrist[1] gave to 648 males and 252 females 2,510 treatments, or an average of 2.7 treatments for each case. Three hundred thirty-nine cases were discharged as improved for the reason that the demand for treatment prevented them from continuing. In many of these cases an additional treatment would have resulted in recovery. One hundred cases were discharged unimproved; for the most part, these were patients suffering from old chronic conditions of long standing and for which chlorin seemed to have no effect. In many instances these cases were suffering from conditions of twenty to thirty years' duration.

The results favorable and otherwise are shown graphically in the chart. (Fig. 2.)

Regarding the concentration and dosage of chlorin gas, Wallace said, a century ago, "Chlorin gas should

(1) Wisconsin Med. Jour., October, 1924.

always be in such quantities as to excite the peculiar sensations which arise from its employment. These sen-

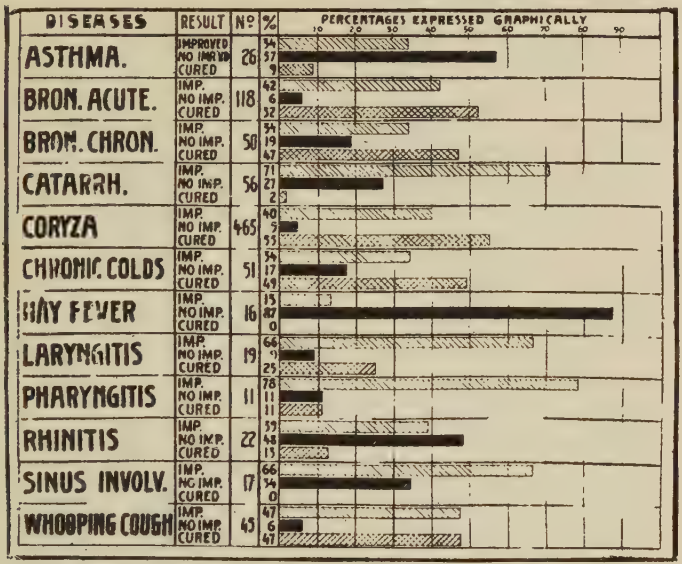


Fig. 2.—Chart showing diseases, result of treatment, number of cases and percentages expressed graphically.

sations will afford the best rule for the regulation of our conduct; and it will be necessary to produce them."

After many experiments, Gilchrist has also found that there can be no set rule laid down governing the actual amount of gas required in a chamber for the reason that there are too many elements entering into it which render it a physical impossibility.

It is a safe rule to follow that any amount of gas "which can be detected by the odor, and which, after an hour's exposure, produces in the individual so exposed a slight irritation in the back of the throat or a slight burning of the eyes, may be considered a safe concentration for general usage. If, on the other hand, the gas produces in the individual exposed an irritation so severe as to cause hacking and coughing, it should be weakened, because these symptoms indicate that the concentration for the particular individual is too strong."

The success of the administration of chlorin gas in the treatment of diseases depends, to a large extent, on the kind of apparatus used.

Since chlorin gas has proved so beneficial in the treatment of human beings, it has also been used by the veterinarians of our army in the treatment of animals. Lieutenants C. S. Williams and F. H. Woodruff, of the Veterinary Corps of the Army, report the use of chlorin gas in the treatment of influenza in 41 animals at Fort Hoyle, Maryland. Twenty-one made complete recoveries after the first treatment and it only required five additional treatments, covering a period of eight days, to cure the remainder.

The chlorin treatment has also been used quite extensively in the city of Washington by different veterinarians in the treatment of distemper in dogs. It has proved very satisfactory.

The dangers in using chlorin gas have been greatly magnified, not alone by the laity, but also by members of the medical profession. Although chlorin gas was used extensively during the war as a weapon of offense, yet, out of 1,843 casualties in our army resulting from its use, but seven, or about one-third of one per cent. were fatal.

Since the chlorin investigation was begun over a year and a half ago by the medical officers of the Chemical Warfare Service, more than 3,500 persons have been treated in government institutions by this method. In addition, many have since been treated in the offices of private physicians. Yet not a single instance is known of a bad result. Persons were interviewed who had been working with this gas for long periods and who at different times were exposed to heavy concentrations, yet in no case were any bad effects reported.

The author concludes that chlorin gas treatment, though not a cure for all respiratory ailments, has a wonderful field of usefulness. The beneficial qualities of this method of treatment depend upon its germicidal action and the stimulation of lymph and blood flow. It

has a curative value in common colds, whooping-cough, influenza and bronchitis, and is well worth a trial in bronchial-asthmatic cases. It is very important that the gas be given in sufficient strength. If too weak it will not produce the desired effects. There is practically no danger whatever in any reasonable dose.

[That this is a panacea for acute infection of the respiratory tract may well be doubted, and the voices of those who have been disappointed in its use are making themselves heard.—Ed.]

Iodin

Iodin Solution in Liquid Petrolatum. P. S. Mitchell[2] recommends one-half per cent. solution of iodin in liquid petrolatum as a very satisfactory antiseptic application. It is prepared by dissolving the iodin in about eight parts of ether and pouring this solution into sterile liquid petrolatum. If it is desired to use the oil in the nose or throat, it may be further diluted with liquid petrolatum. If an ointment of iodin is desired, which is considered a very efficient method of applying iodin to the surface, a jelly may be made by melting petrolatum and adding the ethereal solution of iodin. For cleansing a wound the author recommends swabbing it with cotton saturated with gasolin. This should be followed by alcohol to prevent the drying effect of the gasolin. Then six to eight layers of gauze impregnated with the iodin oil solution are applied directly to the wound. The dressing should be changed every twelve hours.

MERCURIALS

Disinfecting Power of Mercuric Chlorid Influenced by Other Ions. Hitherto it has been assumed that the reason for the superiority of mercuric chlorid over mercuric bromid and mercuric cyanid is due to the greater

(2) Jour. Kansas Med. Soc., January, 1924.

ionization of the former. Likewise, when increasing quantities of sodium chlorid are added, there is a progressive diminution in the disinfecting power running parallel to the formation of the complex salt $Hg\ Cl_4Na_2$ and diminution of the number of free mercury ions.

That, however, another factor must be of importance E. Krahé[3] points out is shown by the fact that in spite of the slighter dissociation of mercuric chlorid it is more powerful than mercuric nitrate, sulphate and acetate. This special position of chlorid the author finds due to its lipoid-solubility in which the chlorid is much superior to all other mercury salts. He also finds that the complex salt produced by the addition of sodium chlorid to mercuric chlorid is lipoid-insoluble.

In connection with this it is of interest to note that the disinfecting power of phenol solution is influenced in the opposite direction by the addition of sodium chlorid which by "salting out" of the phenol, increases its lipoid-solubility.

Clean Mercurial Inunction in Syphilis. H. N. Cole, J. G. Hutton and Torald Sollmann[4] report a further series of cases which entirely confirm the conclusions of their first series (1921) and establish beyond any doubt that mercurial inunctions are fully as efficient when the excess of ointment is removed with benzin, after thirty minutes of rubbing, as when the ointment is left on the skin. By either method, about half of the patients require from eleven to nineteen rubs before salivation occurs; about a fourth require a smaller, and a fourth a larger number. Pathologic conditions of the skin are important factors in the absorption of the inunction.

Mercury Suspension. H. N. Cole, J. G. Hutton, John Rauschkolb and Torald Sollmann[5] studied the effects of intravenous and intramuscular injection of "*mercodel*", a fine trituration of mercury with glucose, in the ratio

(3) Klin. Wochenschr, Jan. 8, 1924.
(4) Jour. Amer. Med. Ass'n., Jan. 19, 1924.
(5) Ibid., Aug. 23, 1924.

of about 1:5. The trituration divides the mercury into very minute particles, said to range "from half the diameter of a blood corpuscle" to the submicroscopic; it also surrounds them with a film which delays their running together when the powder is suspended in water. For clinical use, the contents of a commercial ampule (0.5 gm. of mercury and 2.43 gm. of glucose) are shaken with 50 c.c. of sterile distilled water. This forms a suspension, isotonic with blood plasma and containing 1 per cent. of mercury. This suspension is strained through a pledget of cotton and is then to be rapidly injected into a vein.

Intravenous injections of such metallic mercury suspension produces marked therapeutic response, manifested by the rapid disappearance of the organisms from the primary lesion, prompt clearing of the secondary lesions, and improvement of the spinal fluid. These effects start within one or two days after the first injection, but the condition relapses unless the treatment is carried further. More than six injections are required for satisfactory results.

The quantity of mercury in a "course" is very much greater than that introduced by any other method. According to current conceptions, a large quantity of mercury would be expected to remain in the body for a year or longer. The injections do not provoke anaphylactoid reactions and appear to have relatively little effect on the kidneys and intestine, but they are likely to cause more or less stomatitis which may flare up suddenly into very severe and fatal forms. The repeated injections that are necessary tend to set up inflammatory reactions in the vein, of such degree as to be seriously objectionable. Until the conditions that influence the toxicity are better known and controlled, the risks appear too great to justify the therapeutic use of these injections.

Intramuscular injections seem to be very painful; the patient may become severely salivated, and the therapeutic effect is not so pronounced.

Mercurochrome—220

Mercurochrome—220 Soluble in the Treatment of Gonorrhea. William von Lackum and Benjamin H. Hager[6] conclude that mercurochrome treatment adds to the potency of the silver compounds and thereby shortens the course and lessens the complications in most instances. They find that: (1) solutions of merchurochrome are very unstable and should not be used if they have stood longer than seventy-two hours; (2) tolerance of the gonococci occurs if the treatment is continuous; (3) solutions ranging from 0.25 to 1 per cent. are just as efficacious as stronger solutions when used in the urethra, and produce no distressing subjective symptoms; (4) mercurochrome is not a substitute for silver compounds, but is most effective when used in conjunction with them.

In the treatment of acute gonorrhea in men they employ during the first week or ten days anterior urethral injections of 0.25 of 1 per cent. freshly prepared solution of mercurochrome, four or five times daily for three days, and then alternate with a 5 per cent. solution of protargin mild (argyrol) for three days. At the end of the latter period, the use of mercurochrome is resumed. During this time, the patient receives office treatment daily, and a 1 per cent. solution of mercurochrome, or a 5 per cent. solution of protargin mild is injected in the anterior urethra, which is promptly followed by anterior and posterior urethral injection of 1 per cent. mercurochrome, or 5 per cent, protargin mild. The former is retained for ten minutes and the latter for from twenty to twenty-five minutes, by means of an ordinary rubber band placed around the glans between

(6) Jour. Amer. Med. Assn., Dec. 8, 1923.

the corona and the meatus. The drug used in the office treatment is the opposite of that used by the patient.

Second Period (week or 10 days). The protargin mild injections are now replaced by 0.5 per cent, protargin strong solution, a 0.5 per cent. solution of mercurochrome being used for alternate periods of three days each. The daily office treatments of anterior and posterior injections of 1 per cent. mercurochrome and 5 per cent. protargin mild are continued.

At the end of the first period there is much less discharge, and the secretion is usually free from gonococci. With the changed treatment, however, an increase in the discharge is often noted in the second period, and often the organisms occur temporarily, the result of the stimulating and desquamative action of the protargin strong. Such increased discharge usually subsides by by the end of the second period, but sometimes the treatment must be prolonged for a few days.

Third Period (stimulation). At this time there are ordinarily no subjective symptoms, and slight, if any, objective phenomena. A small sound is passed for the purpose of making a background over which to express the urethral follicles, and to flatten out granulations. This is followed by the slow injection into the anterior and posterior urethra of 1 per cent. silver nitrate solution, which is massaged lightly into the tissues. Repetition of this form of treatment depends on the recurrence or absence of symptoms. In the absence of symptoms, the treatment is repeated with sounds of increasing size and on intermittent days by catheter (Diday method) irrigations of weak, warm potassium permanganate, to which a little weak silver nitrate solution is occasionally added. During this period, the prostatic secretions should be expressed for examination, as infection of the prostate follicles usually takes place, and massaging the prostate slightly at this time usually prevents future trouble to the gland.

Fourth Period (irrigations). Resolution rapidly takes place at this stage, and the urine is carefully watched. If a few specks remain, an occasional sound, and possibly the injection of a 1 per cent. silver nitrate may be necessary. Further light expression of the prostate may sometimes be required. Increasingly weaker hot potassium permanganate Janet irrigations are continued daily. If the condition seems somewhat resistant, anterior and posterior Kollman dilators may be passed and the urethra dilated to 33 or 35 F., after which a urethral injection of 1 per cent. silver nitrate is given. In the absence of reaction, the hot irrigations are continued for several days, and the patient is dismissed from observation. Their experience leads them to believe that if the foregoing treatment, terminated with mechanical, chemical and instrumental stimulation, does not produce evidence of infection, any remaining organisms are so attenuated that the improved bodily resistance will soon destroy them.

Patients with early chronic gonorrhea as a rule have already had too much treatment with protargin mild, and therefore do not respond well to its use. It is probable that a tolerance is developed on the part of the organisms for the same drug if continuously used. Protargin strong and mercurochrome to the urethra, with local care of the urethral adnexa, appear to fulfil a real need in these cases. When used alternately for periods of three days, the protargin strong sets up a desquamative form of urethritis, eliminating much of the superficial layer of the mucosa, which is already much lower in resistance and allows the mercurochrome to penetrate into a much healthier and more resistant tissue, the organisms of which seem to respond well to the action of mercurochrome. The discharge of urethral origin usually disappears within a comparatively short time. If it persists, the urethral adnexa will usually be found to harbor infection, and prompt response will result from additional massage of the prostate, vesicle strip-

ping, light dilation with a Kollman dilator, and massage of the urethra over sounds, followed by a few injections of silver nitrate alternated with mercurochrome. Cystourethroscopic examination should always be made in resistant cases. In addition to local treatment, hydrotherapy is most important. Patients should drink large quantities of water, and are greatly benefited by local pelvic hyperemia produced by sitz-baths and rectal douches. They recommend that the patient sit in a tub of hot water for from three to five minutes twice a day, and have a rectal douche of half a pint of hot water once a day retaining it for twenty minutes.

In the treatment of gonorrhea in women during the acute stage, the authors begin by swabbing the cervix and vault with tincture of iodin, or a 2 per cent. solution of silver nitrate. This produces a profuse desquamation and discharge, after which the protargin mild and mercurochrome treatment is begun. The vagina is wiped dry, pure crystals of mercurochrome are placed in the os of the cervix, and the vault is swabbed out with 1 per cent. freshly made mercurochrome solution. This is alternated daily with protargin mild crystals in the os, and swabbing out of the vagina with 5 per cent. protargin mild solution. The urethra is injected daily, alternating with 0.5 per cent. mercurochrome and five per cent protargin strong. The patients are instructed to use hot weak solutions of potassium permanganate as a douche from two to four times a day, and to sit in a tub of hot water five minutes each night and morning. This treatment is continued for approximately two weeks, after which it is alternated daily with weak solutions of silver nitrate and 5 per cent. solutions of protargin strong to the cervix and vault. The daily douches are changed from potassium permanganate to warm iodin solution (3.75 c.c. of the tincture of iodin to 1,000 c.c. of water).

E. Rupel[7] obtained more favorable results by the use of stronger solutions (five per cent.) of mercurochrome than from weaker ones. He agrees with von Lackum and Hager in believing that the use of the dye alone did not give as uniformly good results as when it was used alternately with one of the colloidal silver suspensions—argyrol or its equivalent. Each morning a small quantity of 5 per cent, mercurochrome-220 soluble was slowly injected with a blunt syringe, and was retained from three to five minutes. When considerable burning was produced, a prescription calling for oil of santal, (0.6 c.c.), three times a day, after eating, was given the patient. On his return in the evening a 25 per cent. argyrol solution was substituted for the mercurochrome. This was a daily routine, and was varied only in the hyperactive cases or in those prolonged and complicated.

Where there was considerable active discharge, the mercurochrome injection produced considerable burning; but this was complained of only at the first visit. This burning rarely lasted longer than twenty minutes, and never was more severe than that accompanying the act of urination which one often sees during a hyperactive stage.

A disappearance of purulent discharge was effected by the third day in 75 per cent. of these cases. Approximately 70 per cent. of the cases reached an apparent cure in one week, and in ten days 75 per cent. were cured.

Incompatibility of Mercurochrome—220 Soluble—with Alkaloids. L. E. Warren[8] finds that the following substances give precipitates: alypin, apothesin, benzocain, butyn, cocain hydrochlorid, B-eucain lactate, phenacain, procain, propaesin, quinin and urea hydrochlorid and stovain, as well as other alkaloids. Aqueous solutions of benzyl alcohol and saligenin, substances

(7) Jour. Amer. Med. Ass'n., Feb. 24, 1923.
(8) Ibid., Apr. 14, 1923.

which have local anesthetic properties but which are not of alkaloidal nature do not produce these precipitates.

Edwin C. White[9] explains this incompatability as follows. The salts of organic bases generally exhibit an acid reaction in solution because of a greater or less degree of hydrolysis. It might, therefore, be expected that these salts, when brought into contact with the sodium salt of a comparatively weak organic acid, such as the soluble form of mercurochrome, would act like any other acid and precipitate the dye. When equal volumes of 5 per cent. procain (a hydrochlorid of an organic base) and 2 per cent. mercurochrome-220 soluble are mixed, a red precipitate, which soon becomes gummy is formed and practically all the dye is thrown out of solution. A saturated solution of codein base gives no reaction with 2 per cent. mercurochrome solution, thus showing the essential part played by the acid part of the alkaloid salt. The precipitation of mercurochrome may with certainty be avoided by refraining from using simultaneously drugs of an acid character. Boric acid is an exception; it is so feebly acid that a saturated solution does not precipitate mercurochrome.

Silver nitrate and zinc sulphate, both of which are used in the genito-urinary tract, produce precipitate with mercurochrome. They may be alternated with the dye, but should not be used concurrently with it. In general, salts of heavy metals will precipitate mercurochrome.

It is suggested that when it is desired to use a local anesthetic with mercurochrome-220 soluble, a 2 per cent. solution of benzyl alcohol be employed. This has been found to be compatible with the dye.

These comments were elicited by the report of Charles E. Stoltz[1] who injected a 2 per cent. solution of mercurochrome-220 soluble into the bladder five minutes after he injected into the bladder 30 c.c. of a 5 per cent.

(9) Jour. Amer. Med Ass'n., Apr. 28, 1923.
(1) Ibid., Apr. 7, 1923.

solution of procain. Three hours later the patient returned unable to urinate. A catheter withdrew urine, together with numerous pieces of solidified mercurochrome. As the process became very painful to the patient, the bladder was filled with 175 c.c. of a 1 per cent. solution of sodium carbonate, which was retained for one hour. He then urinated freely, and the solution was highly crimson with dissolved mercurochrome. The bladder had to be irrigated twice a day for three days before the solution remained colorless.

Mercurochrome—220 Soluble Intravenously in Chronic Gonorrhea. W. A. Whitman[2] reports ten patients suffering from chronic gonorrhea, placed on intravenous mercurochrome treatment. The dosage was regulated according to the physical condition and body weight, and was given in gradually ascending amounts in most cases. The lowest and highest initial doses were 2 and 5 mgm. for each kilogram of body weight, respectively, administered in 1 per cent solution. The size of the dose apparently did not determine the severity of the reaction, which was manifest by chill, nausea, occasional emesis, joint pains and fever. The febrile reaction sometimes amounted to 105° F., but invariably reached its crest by the sixth hour after injection. Injections were repeated daily or every other day until a satisfactory result was obtained or stomatitis set in, which was usually regarded as a signal for the termination of mercurochrome treatment.

The average total amount of mercurochrome administered was 9.6 mgm. for each kilogram of body weight.

The average time required for the complete disappearance of pus, in cured cases, was eight days. Six patients were discharged as cured at the expiration of mercurochrome therapy. In two cases, a brief resumption of local antisepsis (eight and eleven days, respectively) was necessary, while the two remaining patients are still under local treatment.

(2) Jour. Amer. Med. Ass'n., June 14, 1924.

The use of the word "cure" in this article is to denote cessation of all accepted symptoms of infections, and the inability to reproduce these symptoms by instrumentation and the injection of 2 per cent. silver nitrate solution into the urethra.

The rapid subsidence of symptoms in all, and the abrupt termination of symptoms in some cases, was almost incredible to one accustomed to the usual slow methods of gonorrheal treatment.

The results obtained are ascribed not only to the germicidal action of the mercurochrome; but probably as well [or mainly—Ed.] to the inhibiting influence of the continued high temperature of reaction.

Intravenous Injection of Mercurchrome-220 Soluble in Sepsis. Animal experiments have shown that up to 5 mgm. for each kilogram of body weight in rabbits and 10 mgm. for each kilogram in dogs, could be injected with impunity and that the urine became either bactericidal or strongly becteriostatic for *B. coli.* during the first five hours after injection. The increase in inhibitive action was not in direct proportion to increase in dosage, which can probably be explained by the fact that, with smaller doses, in rabbits from 1 through 5 mgm, for each kilogram, most of the drug is eliminated through the kidneys, whereas with higher doses there is diarrhea and intestinal elimination. J. H. Hill and J. A. C. Colston[3] have also shown that, after the intravenous administration of mercurochrome to normal rabbits, the blood is strongly bacteriostatic for *B. coli* from fifteen through forty-five minutes after injection.

Hugh H. Young and Justina H. Hill[4] report seven desperate cases of infection treated by mercurochrome including two cases of septicemia in which cure was effected and the blood sterilized by intravenous injection of mercurochrome. "The results were almost miraculous, the patient being verily snatched from the jaws of death."

(3) Johns Hop. Hosp. Bul., November, 1923.
(4) Jour. Amer. Med. Ass'n., Mar. 1, 1924.

In an ascending retroperitoneal infection, the disappearance of the inflammatory mass was just as startling. In two cases of pyonephritis, the patients' lives were undoubtedly saved, and in two cases pronounced *B. coli* urinary infection of the kidney and bladder disappeared almost immediately after a single injection of mercurochrome. In most of these cases, the organism has been one of the colon group, but one of those reported here was a staphylococcus septicemia with extensive infectious processes in the chest, back and arm. Other cases in which the drug was administered by others show that mercurochrome may be efficacious in streptococcus septicemias as well as in those due to the staphylococcus and colon bacillus. The authors, however, have treated several septicemias (two *S. hemolyticus* and two *S. viridans*) without success.

In one case, a child, a dose of 8 mgm. for each kilogram of body weight was used once, and in one adult they injected 6.8 mgm. for each kilogram; but the patient had very severe nausea, vomiting and diarrhea, with a transitory albuminuria. Other patients who received 5 mgm. for each kilogram had pronounced gastro-intestinal symptoms, but all were transitory and after a few days the patients were normal. In urinary infections, the smaller dose may be justified and perhaps just as efficacious; but the desperate nature of septicemia demands drastic treatment, and 5 mgm. for each kilogram should be employed. That the drug is not always successful in sterilizing the urine has already been pointed out.

Salivation Due to Mercurochrome. J. C. Bunten[5] reports two cases in which very pronounced salivation developed. In one case 10 c.c. of a 2 per cent. solution was given intravenously and in 48 hours this dose was repeated. Two days later the patient had pronounced salivation, loose teeth, bleeding gums and pain. In about a week this condition cleared up. In another case 10 c.c.

(5) Jour. Amer. Med. Ass'n., May 3, 1924.

of a 1 per cent. solution of mercurochrome intravenously repeated in 48 hours was followed in two days by a very severe salivation, all the teeth loose, the gums spongy, the patient suffering a great deal with aching of all the teeth. The condition also cleared up in a week.

In both of these cases, the results from the use of the mercurochrome, as far as the original pathologic condition was concerned, seemed to be very satisfactory, though the salivation proved very distressing for a time. The author is of the opinion that the intravenous use of mercurochrome-220 soluble in septic cases is worthy of trial, especially in grave cases, but one will have to bear in mind the possibility of salivation for a time. These patients always have a reaction following the doses, and the reaction following the first dose is always greater than the succeeding ones. Usually there is headache, increase in temperature, perspiration, and frequently nausea and vomiting.

Chester C. Gus[6] reports a case of stomatitis developing after the injection of 15 c.c. of a 1 per cent. solution of mercurochrome-220 soluble into a tuberculous sinus, repeated daily for nineteen days with marked improvement, when the patient began to complain of soreness in the gums, profuse salivation, loosening of the teeth, and diarrhea. These symptoms increased rapidly in severity. Two weeks later, the stomatitis and diarrhea had entirely disappeared, and they have not recurred since.

Dosage of Mercurochrome-220 Soluble. John W. Visher[7] calls attention to the fact that salivation occured in most cases only after prolonged use of the drug in fairly large doses. Guy, for example, injected 15 c.c. of 1 per cent. solution into a tuberculous sinus for nineteen days (a total of 2.85 gm.) before salivation occurred. It has been Visher's experience that smaller

(6) Jour. Amer. Med. Ass'n., June 28, 1924.
(7) Ibid., Aug. 2, 1924.

doses than those suggested by Young and Hill are often effective. In a series of three cases of epidemic encephalitis very prompt recovery followed small doses of mercurochrome. In one case, only 10 c.c. of 1 per cent. solution (1.5 mgm. for each kilogram) was given, while in the other two cases two injections of 10 c.c. each were used at twenty-four hour intervals. Improvement had begun before the second injection in both cases, so that the second 10 c.c. may have been unnecessary. No febrile reaction or salivation occurred in this series of cases. The author believes that, in the intravenous administration of mercurochrome, small doses should be given first in all but the most desperate cases. If not effective, larger doses should be tried in spite of the risk of salivation.

SILVER

Silver Nitrate in Vasomotor Rhinitis. French K. Hansel* reports that satisfactory and gratifying results, from the standpoint of both patient and the physician, have been obtained by the use of silver nitrate in concentrations of from 12 to 50 per cent. applied by means of a cotton applicator to the region of the sphenopalatine ganglion, preceded by 10 per cent. procain solution, applied with a cotton applicator, and permitted to remain in position about five minutes with the 12 per cent. solution, and from five to ten seconds with the 50 per cent. solution. Within a few hours a paroxysm of sneezing, lacrimation, watery discharge and nasal obstruction occurred, which lasted from two to 24 hours. Immediately after the subsidence of the attack it was found that 50 per cent. of the patients were markedly or completely relieved; the remainder were only slightly relieved or their condition was unchanged.

(*) Jour. Amer. Med. Ass'n., Jan. 5, 1924.

The results following the intranasal applications have been superior to those obtained by other forms of treatment.

Protargin Strong of Little Value as a Preoperative Antiseptic. A. B. Reese[8] attempted to determine the effectiveness of the preparation of the eye for operation at the Massachusetts Charitable Eye and Ear Infirmary by taking cultures before and after preparation in 40 cases. The routine preparation of the eye at this hospital consists of the instillation of 4 per cent. protargin strong as soon as the patient is brought to the operating room. Then a wide region surrounding the eye is painted with a 2 per cent. iodin, including the eye brow and lid margins. The conjunctival sac is then irrigated with saturated solution of boric acid. In cataract cases, the conjunctival flap is made before the irrigation with boric acid solution. The protargin strong remains in the conjunctival sac about five minutes or less before it is irrigated with boric acid solution.

Although positive cultures were obtained in twenty-six cases, or 65 per cent., after the preparation was completed, not one of these cases, or any of the forty cases, showed infection following the operation. In fifteen cases, the unoperated eye was simply irrigated with physiologic sodium chlorid solution without instilling any protargin strong. The results were just the same as in those cases in which protargin strong was used.

Experiments were done on rabbits in whom a suspension of staphylococci in distilled water was instilled into the conjunctival sac of both eyes. After about three quarters of an hour, fresh protargin strong, 4 per cent., was instilled into the conjunctival sac of one eye over a period of eight minutes. The sac was then irrigated with one bulb of physiologic sodium chlorid solution, and a culture was taken. The other eye, which had no protargin strong, was simply irrigated with one bulb of

(8) Jour. Amer. Med. Ass'n., May 17, 1924.

physiologic sodium chlorid solution, and a culture was taken. For all practical purposes, the cultures from the two sides showed equal growths. In other words *one can obtain just as great a reduction of organisms by mechanical irrigation of the sac.* Infecting organisms are for the most part intracellular and these are probably not to be reached by antiseptics and very few by irrigation.

Antiseptic Efficiency of Protein and Colloidal Silver Compounds Much Diminished by Defibrinated Blood. J. D. Pilcher and Torald Sollmann[9] using the yeast method, which furnishes a convenient and sufficiently accurate measure of the concentration of the silver ions in solutions, studied the influence of blood on the antiseptic action of various types of silver compounds, the blood being intended to represent the conditions of secretions or fluids rich in proteins and cells, such as pus or wound secretions. It was found that these interfere with all classes of silver compounds. For the inorganic silver salts, the interference of blood is somewhat less than that of normal saline; for the silver-protein compounds, the interference of blood is considerably more than that of normal saline.

Colloidal Silver, Fate in System. After intravenous injection of argochrom, electrocollargol or collargol, H. Schlee and E. Zweifel[1] found silver in the blood in every case after 30 to 60 minutes. The concentration of the silver ion in the defribinated blood or serum was nearly always the same regardless of the quantity of the silver administered. The balance of the silver must be deposited in the tissues.

Argyria Due to Argyrol. T. D. Davis[2] reports two cases of argyria due to argyrol. One of the patients had used a nose and throat spray of 25 per cent. solution of argyrol for several months. The other had been using argyrol solution on the gums frequently for years.

(9) Jour. Lab. and Clin. Med., Jan. 4, 1924.
(1) Zeitschr. f. Hyg. u. Infektionskrankh., p. 457, 1924.
(2) Virginia Med. Monthly, June, 1924.

ARSENICALS

Transmission of Arsenic from Mother to Fetus. Frank P. Underhill and Frank G. Amatruda[3] detected arsenic in small traces in the fetal tissues after the intravenous injection of neo-arsphenamin into the maternal circulation. The amount of arsenic recovered from the fetal tissues does not increase in proportion to the number of serial injections given. On the other hand, arsenic is stored in the maternal liver and placenta, the amount increasing with the number of injections. The fact that arsenic is not stored in the fetal tissues is of considerable clinical importance. The drug can be safely administered in the antenatal treatment of syphilis, in the ordinary doses given to men and non-pregnant women, without any danger of its having a toxic effect of the fetus. The explanation offered for the efficiency of antenatal treatment of syphilis, especially on the newborn, is that the spirocheticide acts in greater concentration and more directly on the spirochetes in the placenta.

Arsphenamin

Prophylactic Use of Arsphenamin. The prophylactic use of calomel ointment or similar chemical agents has proved efficacious only when employed within about eight hours after cohabitation. When a longer interval has elapsed the use of arsphenamin as advocated by Michel and Goodman (1920) is of interest. In cases in which one of the persons concerned has had intercourse with a frankly syphilitic partner, four to six arsphenamin injections of not more than 0.3 gm. at intervals of two to five days seemed to protect the exposed person. Adolph Rostenberg[4] reports an additional case in which four neo-arsphenamin injections kept the patient well and the Wasserman reactions negative.

(3) Jour. Amer. Med. Ass'n., Dec. 15, 1923.
(4) Ibid., Jan. 19, 1924.

Calcium Arsphenamin Therapy. In the belief that a disturbance of the equilibrium between calcium and potassium ions is of importance in the development of arsphenamin intolerance, F. Jacobsohn and Sklarz[5] advise dissolving neo-arsphenamin in sterile 10 per cent. calcium chlorid solution (such as for instance is marketed in 5 c.c. ampules by Merck) instead of using sterile water in all those cases in which the remedy administered in the ordinary way is not well tolerated and in those patients which have had a previous treatment with other ions such as Hg-Au-Bi.

The authors base this recommendation upon animal experiments which showed that minute doses of potassium administered with otherwise harmless doses of arsphenamin produce death in rabbits, while on the other hand, sufficiently large doses of calcium paralysed the fatal summation of arsphenamin-potassium action. They also call attention to the great increase in arsphenamin intolerance which was observed in Central Europe during the war which they ascribe to the predominantly potassium rich vegetable diet of that time. The authors report six cases from their experience which show the advantage of the combination recommended.

When using the combination advocated, aspirating of blood into the syringe is to be avoided as fairly large blood clots may thus be produced. The injection should be given very slowly, and the patient should be apprised of the fact that he is likely to experience a momentary sensation of heat occurring after the beginning of the injection and disappearing quite as rapidly.

Rectal Administration of Arsphenamin Unsatisfactory. As the result of a clinical study, Sidney Littman and J. G. Hutton[6] find that the results obtained by the rectal use of arsphenamin in acute manifestations of congenital syphilis are too feeble when compared

(5) Klin. Wochenschr., July 8, 1924.
(6) Jour. Amer. Med. Ass'n., Mar. 15, 1924.

with the intravenous or intramuscular results, to warrant the consideration of this method in the treatment of congenital syphilis.

The absorption of arsphenamin from "Supsalvs" suppositories, even when given twice daily, to patients with primary and secondary lesions of syphilis, is not sufficient to destroy the spirochetes in the lesions or to exert any noticeable favorable influence on the eruption or the course of the disease. Hence the intravenous administration of arsphenamin should be preferred to rectal administration as being more successful and more efficient. Moreover, both neo-arsphenamin and sulpharsphenamin are now used generally by the intramuscular route in the treatment of syphilis in infants, the results being above reproach.

Sulpharsphenamin

Sulpharsphenamin Administered Intramuscularly in Syphilis. John H. Stokes and Claude W. Behn[7] report that sulpharsphenamin given intramuscularly has proved to be quite as effective therapeutically as arsphenamin and neo-arsphenamin from the standpoint of spirillicidal action and of the effect on the blood Wassermann and spinal fluid reactions, on the healing of lesions, and on the general well-being of the patient. They believe it is superior in the treatment of neurosyphilis to the older drugs, and to neo-arsphenamin intravenously in all aspects of syphilis. The drug is well borne by patients with cardiovascular disorders, if used in moderate dosage. There is a distinctly increased tendency to cutaneous reaction as compared with the more familiar arsphenamins.

The present report includes 126 patients with all types of syphilis who received intramuscularly 1,360 injections, ranging from 0.3 to 0.6 gm. each. It was injected by the "epifascial" technic described by

(7) Jour. Amer. Med. Ass'n., July 26, 1924.

Stokes, practically without significant local reaction, and with no more discomfort than attends the ordinary mercurial injection intramuscularly. Doses over 0.4 gm. should be divided between the two buttocks. The authors believe subcutaneous injection to be less effective therapeutically, and do not advise it. Even with the inclusion of the most trifling reactions, such as a stinging sensation, no local discomfort whatever occurred in 83 per cent. of the 1,360 injections. Two objectively visible reactions developed, one an infiltrated plaque, which subsided under hot applications, and the other a sterile abscess, which caused no symptoms and which the patient did not know was there. Emphasis should be placed on using a 30 to 40 per cent. solution; on complete emptying of the 2 c.c. syringe by having a small bubble of air above the injection fluid to clear the needle, and on the use of a correct epifascial technic. Only one patient was transferred to other treatment because of a local reaction.

D. L. Belding[8] finds that sulpharsphenamin produces a greater proportion of toxic disturbances than neo-arsphenamin. Dermatitis occurred in 16 per cent. of the patients. Varying degrees of peripheral neuritis occurred in 56 per cent. of the adult patients. Though for intravenous medication, sulpharsphenamin possesses the advantage of convenience in administration over arsphenamin and of a more stable solution over neo-arsphenamin, the frequent production of toxic effects renders it less satisfactory for intravenous therapy than the other arsphenamins. Sulpharsphenamin is well suited for intramuscular injections in adipose women, children and other patients when the intravenous route is difficult or impossible. Its promiscuous administration under the impression of its low toxicity is open to criticism.

Sulpharsphenamin in Vincent's Angina and Stomatitis in Children. L. H. Barenberg and M. W. Bloom-

(8) Jour. Derm. and Syph., April, 1924.

berg[9] have treated fifteen cases of Vincent's angina, eight by intramuscular injections alone and seven by intramuscular injection combined with local application of sulpharsphenamin three times daily. The dose was 0.1 or 0.2 gm.; five received one injection of 0.1 gm., two children received two injections of 0.1 gm., and only one required two injections of 0.2 gm. Five had one intramuscular injection as well as local applications for three days. No patient required a second injection. The average duration of disease in those patients, who simply were injected, was six and one-half days; of those on combined treatment, in whom 0.2 gm. of sulpharsphenamin was given, about four days.

Twenty-seven cases of stomatitis likewise were treated. Of these, nineteen were typical cases of ulceromembranous gingivitis. Some of these were treated simply by intramuscular injections; in others, this method was combined with local applications of sulpharsphenamin. In the former group, the lesions took about one week to heal, and in the latter, in which local applications reinforced systemic treatment, the gums resumed a normal appearance in about five days. Such results are superior to those which the authors encountered in the course of a somewhat extensive experience with this type of case. In some instances, pyorrhea alveolaris also responded to these measures.

The sulpharsphenamin was dissolved in the ampule in the concentration of 0.1 gm. to 5 minims of distilled water. A little shaking is necessary for quick solution. A medium sized needle, about 18 gage, is used, and the injection is given in the buttock. In the course of 51 injections of sulpharsphenamin, no general or local reactions of any kind have been noticed. As intravenous medication is difficult in children, this mode of therapy is particularly suitable to them.

(9) Jour. Amer. Med. Ass'n., July 5, 1924.

Tryparsamid

Tryparsamid in Syphilis. Joseph Earle Moore, Harry M. Robinson and Richard S. Lyman[1] present the results of treatment in 195 patients, of whom 133 are neurosyphilitic, observed during the last four years. In neurosyphilis they administer tryparsamid in weekly intravenous injections, in an average adult dose of 3 gm. A course comprises from eight to sixteen injections.

They conclude that in primary and secondary syphilis, or in tertiary syphilis without nervous system involvement, the therapeutic effect of tryparsamid is so slight as to preclude its further general use in these types of infection. In neurosyphilis, on the contrary, tryparsamid therapy produces favorable clinical and serologic results, which they believe cannot be equaled by other forms of treatment. This drug is of particular value in early general paralysis, in meningovascular neurosyphilis, and in the majority of cases of tabes. Advanced general paralysis is benefited little, if at all.

In early neurosyphilis, the comparatively feeble spirocheticidal value of tryparsamid precludes its use unless in combination with an arsphenamin.

Visual disturbances following tryparsamid have occurred in 17.8 per cent. of a series of 241 cases; but in only 2.8 per cent. has noteworthy permanent visual injury resulted. Hence, to prevent serious damage to the eyes from tryparsamid every patient should be examined by a competent opthalmologist as to visual acuity, fundi, and especially visual fields. Reëxamination must be carried out at the first appearance of subjective visual disturbance, and visual acuity and fields compared with those noted before treatment. At this point, objective injury, if present, is usually so slight as to leave useful vision if the drug is permanently withdrawn. The treatment of patients whose

(1) Jour. Amer. Med. Ass'n., Sep. 20, 1924.

mental condition is too dilapidated for coöperation, or the continuation of therapy after changes in visual acuity or fields have occurred, is dangerous.

The danger of visual impairment, however slight, combined with the comparatively poor results of tryparsamid therapy in types of syphilis other than neurosyphilis, leads the authors to feel that *the general use of the drug ought strictly to be limited to neurosyphilis and trypanosomiasis.*

Harry C. Solomon and Henry R. Viets[2] also consider tryparsamid an important addition to our antisyphilitic drugs. They employed tryparsamid during a period of eleven months in about 100 cases of neurosyphilis of various types giving intravenous injections of 3 gm. at weekly intervals. No immediate reactions of serious nature were encountered. Four patients, however, developed a considerable degree of amblyopia, in three of which a permanent defect remained. Mild and fleeting amblyopia were also encountered.

The effect on the pleocytosis in the spinal fluid was very striking. In nearly every case, the cell count was reduced to normal after six or eight injections. These results were obtained, moreover, in some cases in which previously much antisyphilitic treatment had been given without developing a normal cell count. Globulin and total protein have been reduced in many cases, but, as a rule, only to a relatively small extent and in but few cases have these tests become negative.

The Wassermann reaction in the spinal fluid has not been greatly affected in the majority of cases, including a number in which more than 30 tryparsamid injections were given. There were, however, a number of striking exceptions in which the Wassermann reaction was made negative, some of these being cases in which long periods of treatment with other methods had failed to accomplish this result. The Wassermann

(2) Jour. Amer. Med. Ass'n., Sep. 20, 1924.

reaction was made negative in about one-half of the cases of tabes dorsalis.

In contrast to the cases in which tryparsamid has apparently been more efficacious than arsphenamin and subarachnoid injections, there were cases in which the latter methods produced better serologic results than tryparsamid.

Clinical improvement has been noted in various types of cases of neurosyphilis treated with tryparsamid. The most pronounced improvement was obtained in the meningovascular cases, but it was no more satisfactory than the authors have been accustomed to obtain with other methods The clinical improvement in cases of tabes dorsalis was not so marked as was the serologic improvement. Indeed, the clinical improvement in these cases was, on the whole, less satisfactory than they were able to obtain by other methods. Some improvement occurred in the cases of general paralysis, but in only a relatively small number. Improvement has not been more satisfactory with tryparsamid than with the older methods of intensive therapy by intrathecal, lumbar, cisternal and ventricular injections.

They conclude that *tryparsamid definitely affects cases of neurosyphilis,* in some instances giving results better than can be obtained by older methods alone, and in other cases not giving as good results. Its ease of administration without any discomfort to the patient is a point of superiority. Its tendency to produce toxic effects on the optic nerve necessitates great caution in its use. They believe that the best results may be obtained by its use in conjunction with other antisyphilitic methods.

J. E. Moore, H. M. Robinson and Albert Keidel[3] relate experience which indicates its value in certain types of neurosyphilis and possibly in cardio-vascular syphilis. In other forms of syphilis, in which the nervous system is not involved, there is no evidence

(3) Jour. Amer. Med. Ass'n., Feb. 16, 1924.

that the drug is of any value, except for its tonic effect in undernourished patients. It appears to be contraindicated in early syphilis because of its comparatively feeble spirocheticidal activity. In tertiary and latent syphilis, also, experience leads to believe that it is inferior to the arsphenamins, and that, if used at all in this stage of the disease, it should not replace the arsphenamins or mercury, but only supplement them. It is emphasized that the use of tryparsamid is to be avoided in all cases in which optic nerve impairment already exists, and it is recommended that during tryparsamid administration close attention be given to the fundus of the eye and the sight.

Tryparsamid in Neurosyphilis. Udo J. Wile and Lester M. Wieder* also arrive at the conclusion that tryparsamid is of great service in causing a profound change for clinical betterment in a certain group of cerebrospinal syphilis cases, notably in some cases of general paralysis, especially of the parenchymatous type in which a considerable degree of deterioration had apparently occurred.

The most striking clinical change noted has been increase in weight, color and general appearance. In nine of the cases, a marked improvement of the mental state of patient has been found coincident with the improvement in the general appearance. In five cases, the treatment by tryparsamid was followed by clinical improvement when other forms of therapy, including intraspinal treatment, had failed.

Gastric crises and the lightning pains of tabes dorsalis have, as yet, not yielded to tryparsamid treatment.

ANTIMONY

Antimony Tartrate in Bilharziasis. F. O. Lasbrey and R. B. Coleman[4] report 4,600 individuals treated

(*) Jour. Amer. Med. Ass'n., Dec. 6, 1924.
(4) British Med. Jour., May 24, 1924.

with sodium antimony tartrate which is thought to be less toxic than the potassium salt. For adult males 0.06 gm. is the initial dose, increased by 0.03 gm. each injection up to 0.15 gm., which is the maximum dose. The injections are given daily for six days and then on alternate days. Weak patients and women and children take proportionately smaller doses. The regular number of injections is twelve, which at full doses makes a total of 1.75 gm., but this depends on the results of microscopical examinations. Unless there is some contraindication the authors continue the course until only "dead" eggs are reported. Approximately 60 per cent. of the patients persisted to the end of the treatment. This considerable number continuing to apply for treatment prove its popularity and efficacy. There is a notable increase in the number of rectal cases applying for treatment. The patients are more willing than formerly to take a full course of injections, and only one in twenty gives up before he has received six injections, instead of one in five as formerly. The mortality among patients taking the course has been reduced by half, and is now only 4.9 per 1,000.

LACTIC ACID

Lactic Acid in Leukorrhea. R. Salomon[5] deprecates the use of disinfectants in the treatment of leukorrhea, as the normal biologic conditions characterized by the presence of acid reaction and acid producing bacilli is thereby interfered with. The aim of all rational therapy for simple leukorrhea should be to restore the faintly acid reaction and produce favorable conditions for the development of the normal vaginal bacilli. He endorses Zweifel's ½ per cent. lactic acid vaginal irrigations, which are so efficient that even in gonorrhea

(5) Klin. Wochenschr., July 15, 1924.

very satisfactory results are obtained within 13 to 17 days. Daily lactic acid irrigations should be considered a hygienic necessity for pregnant women with pathologic vaginal secretions during the last two weeks before confinement. The author is at present experimenting with a vaginal injection of a few c.c. of milk which he believes give very promising results in simple leukorrhea. Of course, in leukorrhea due to constitutional or uterine disease or to pathology of the adnexa such treatment would be useless.

PHENOL

Phenol Treatment of Erysipelas. In the 1923 annual report of the medical department of the United Fruit Company[6] is noted a treatment of erysipelas that is attended with excellent results. It consists of swabbing with phenol and then neutralizing with alcohol as soon as a white coating appears. The temperature usually dropped to normal within three to six hours. The same treatment is used for herpes zoster, with equally excellent result.

SALICYLATE

Massive Doses of Salicylate in Acute Articular Rheumatism. D. Daniélopolu[7] believes failure in the treatment of inflammatory rheumatism is due to insufficient doses of salicylate. Sufficiently large doses of salicylate are the specific remedy for the inflammatory lesions, if the treatment is started in the first days of the infection. Arthritis can be cured completely at any time of the disease, cardiac lesions only in the first days

(6) Jour. Amer. Med. Ass'n., July 5, 1924.
(7) Presse Méd., Dec 15, 1923.

of the inflammatory process. He regards sodium salicylate superior to any other preparation. Ill effects like gastric disturbance, tinnitus, dyspnea, delirium, coma and cardiac accidents are due to an intense acidosis produced by the salicylic acid. To prevent these, it is absolutely necessary to add large doses of sodium bicarbonate. The quantity generally used is far insufficient. The patient's urine must be made alkaline. The author advises to add to each gm. of salicylate 2 gm. of sodium bicarbonate. He states that patients with ill effects after the usual dose of 2 to 4 gm. salicylate and an insufficient dose of sodium bicarbonate, tolerated without any inconvenience doses as large as 20 gm. and more daily, if a sufficient quantity of bicarbonate—twice the amount of the salicylate—was added. He advises to dilute each dose with 100 gm. of water to make it better tolerated. [Seltzer water is best.—Ed.] He is strongly opposed to the usual solutions containing alcohol or syrup. The alcohol makes the bicarbonate insoluble, and the patient gets an insufficient quantity of bicarbonate from the filtered solution.

The author used in the average cases with very good result 15 to 18 gm. of salicylate and 30 to 36 gm. of bicarbonate daily; and in severe cases up to 25 to 30 gm. of salicylate and 50 to 60 gm. of bicarbonate daily. Children tolerate still larger doses in comparison to their body weight; those of eight to twelve years were treated with daily doses of 10 to 15 gm. of salicylate.

The treatment starts in the first days of infection, has to be progressive and prolonged according to the symptoms. Equal fractional doses are given every 2 hours during the day and every 4 hours during the night. The author emphasizes to be strict in this respect and never miss awakening patients. The initial dose for the adult is 8 gm., for children eight to twelve years 5 gm., below that age 2 to 3 gm. daily. This quantity is given for two days, then if no improvement is noted, the dose is increased progressively from 1 to 2 gm. daily

until the improvement commences. The dose reached at that stage is kept up constantly till the articular symptoms and the fever have nearly disappeared. From this time on the dose is gradually diminished, but never more than 1 to 2 gm. every second day. If fever or articular symptoms recur one has to return to larger doses immediately. In cases of gastric disturbance, the treatment is interrupted from 6 to 24 hours. Diarrhea can easily be corrected by 1 to 2 gm. of laudanum. During the whole course of treatment each dose of salicylate is followed by ingestion of some nourishment. The diet consists principally of cereals and sweets. A certain quantity of milk can be added. The patient has to be kept in bed till all symptoms have disappeared and better still longer. The treatment lasts in the average about 45 days, in severe cases longer.

Cases in which cardiac lesions occur in the course of the disease, are no contraindications for large doses of salicylate; neither are chronic cardiacs with an acute attack of rheumatism. For the latter, combination with digitalis is often advisable.

Leukocyte Curve as an Indication for Continuance of Antirheumatic Medication. After the usually prompt subsidence of the symptoms of rheumatic fever under salicylate medication, the physician is faced by the problem of the further duration and dosage required. In this we may possibly be helped by the observation of C. P. Miller, R. H. Boots and H. F. Swift[8] who found that, when the leukocyte curve fell to normal and remained there, the patients went on to recovery without relapse, whether treated by antirheumatic medication or not. When the curve remained above from 12,000 to 14,000, or, when after the institution of antirheumatic treatment an initial fall was followed by a rise, withdrawal of the drug was always followed by a definite clinical relapse.

(8) Jour. Amer. Med. Ass'n., June 14, 1924.

HEXYL RESORCINOL

Hexyl Resorcinol ("Caprokol"), a Urinary "Disinfectant." In 1913, Treat B. Johnson synthesized a number of the lower homologues of a series of alkyl resorcinols which were examined as to their bactericidal properties by Leo. Rettger who found a very rapid increase in the phenol coefficient as the series was ascended. The compounds have been studied biologically since 1914 by Veader Leonard* who finds that the peak of bactericidal power is reached with the n-hexyl derivative, which exhibits a phenol coefficient of 46, having the bactericidal power of resorcinol multiplied over 150 times. All of these substances may be administered by mouth to rabbits in large doses (1 gm. per kilogram) without apparent toxic effect. Bactericidal urine was obtained not infrequently in rabbits after oral administration of each of seven alkyl resorcinols tested, but in this regard also n-hexyl resorcinol was found to be so far superior to the lower homologues that detailed discussion is limited to this substance.

Hexyl resorcinol retains its bactericidal power when dissolved in urine of either acid or alkaline reaction, destroying *B. coli* in 1:10,000 dilution within one hour, and *Staphylococcus albus* in dilutions of 1:60,000.

On doses of from 0.25 to 0.5 gm. of hexyl resorcinol three times a day, normal men secrete urine which kills *B. coli* and *Staphylococcus albus*. On doses of less than 0.25 gm. three times a day, the secretion of bactericidal urine was only occasional. Marked individual variation was shown on 0.33 gm. doses.

The crystals have been administered in enteric coated capsules to avoid gastric irritation, the doses varying from 0.33 to 1 gm. three times a day. The first few doses of hexyl resorcinol frequently show a decided cathartic action due, no doubt, to intestinal irritation. This effect usually disappears within 48 hours, although it may last much longer. It has proved to be a serious

(*) Jour. Amer. Med. Ass'n., Dec. 20, 1924.

disadvantage in a few cases, necessitating a material reduction in the dose. On the other hand, patients who have been habitually constipated have volunteered the information that daily spontaneous evacuation of the bowels has occurred while under treatment. Some patients tolerate doses as high as 4 gm. a day, but this quantity ordinarily causes marked intestinal irritation.

Although hexyl resorcinol is secreted promptly, and certainly, in large part, in the urine, it is apparent that the bulk of each dose appears in the urine in an inert form. This is indicated by the fact that the concentration of substances in the urine giving the characteristic red color with nitric acid does not indicate the degree of bactericidal power shown by that specimen. In fact, a urine specimen showing a brilliant test may be quite inert, while one yielding only the faintest color or none at all may be actively bactericidal (rabbits). The explanation lies in the fact that by far the greater portion is secreted as a conjugate which is inert but yields the color test. We depend, for the bactericidal action in the urine, on the small amount of hexyl resorcinol secreted unchanged. If we could prevent conjugation, very tiny doses would be sufficient. As a matter of experience, large doses, such as from 1 to 2 gm. a day, are indispensable.

The results to date justify the following statements regarding the use of hexyl resorcinol as an internal urinary antiseptic in chronic urinary tract infections in adults.

(a) In urinary tract infections due to *Staphylococcus albus, Staphylococcus aureus,* the streptococcus and some strains of *B. Pyocyaneus,* oral administration of hexyl resorcinol, without other treatment, has resulted in prompt and complete disinfection of the urinary tract, with consequent clearing of the urine and disappearance of symptoms. No recurrences have been observed after several months without treatment.

(b) Urinary tract infections due to *B. coli* have been cleared up completely with no other treatment than hexyl resorcinol by mouth, and have not recurred on discontinuing treatment for several months. Persistent treatment is usually necessary in these cases even when the bacterial count is low. Cases with high counts of *B. coli* in the urine are extremely resistant even to intensive courses of the drug, and it is highly probable that in this type of case the usual local treatment will be found necessary in order to reduce the number of bacteria present to a point which will afford the drug an opportunity to complete the disinfection. Evidence is increasing that failure on the part of hexyl resorcinol to complete the disinfection of the urinary tract in these cases indicates the existence of pyelonephritis.

(c) In mixed infections of the urinary tract with *B. coli*, together with any of the foregoing organisms, the urine has shown a pure culture of *B. coli* shortly after the starting of treatment, all other organisms having been killed off.

(d) There may be pronounced symptomatic improvement on doses which are too small to complete the disinfection.

Although hexyl resorcinol retains its bactericidal power in alkaline urine, the administration of sodium bicarbonate completely prevents the secretion of bactericidal urine.

DYES

In General

Alkali Increases Antisepticity of Dyes. V. Burke and I. Grieve[9] find, as a result of an experimental study, that the bacteriostatic and bactericidal action of dyes is, with but few exceptions, increased with an increase in alkalinity. Hence the body fluids should be made alkaline by the administration of sodium bicarbonate or

(9) Amer. Jour. Med. Sci., July, 1924.

application of an alkaline wash before the dye is applied. This is true of the following dyes: crystal violet, methyl violet, gentian violet, brilliant green, basic fuchsin, the flavines and malachite green.

Pyoktanin

Pyoktanin in Plaut-Vincent Angina. Wickels[1] recommends painting the ulceration with a 10 per cent. solution of Pyoktanin which has proved the best among the local disinfectants tried by him. This is followed by gargling with hydrogen peroxid solution. The ulcers became clean even after the first or second painting.

Gentian Violet

Gentian Violet as Antiseptic Against Gram-Positive Bacteria. J. Shelley Saurman[2] reports sufficiently encouraging results in a number of chronic carriers of diphtheria to warrant further study of the method used by him. The patient, on awakening, and immediately after the three main meals of the day and once during the evening, should have the nares and the fauces well flushed and cleansed with a light saline solution, to rid this region of as much mucus as possible. This may be done by a spray, or by douching by the patient or by an attendant. Immediately after this, the nares and fauces are well sprayed with a 2 per cent. aqueous solution of gentian violet in the ordinary atomizer. After each spraying, the fauces should be inspected to see that the dye has reached every part that can be seen. The dye, though staining everything with which it comes in contact, will not leave any permanent discoloration of the skin, mucous membrane or teeth. Within 24 to 48 hours negative cultures have been obtained.

(1) Therap. d. Gegenw., No. 7, 1924.
(2) Jour. Amer. Med. Ass'n., July 26, 1924.

Gentian Violet Intravenously in Sepsis. Hugh H. Young and Justina H. Hill[3] report five cases of desperate staphylococcus sepsis treated with brilliant results by intravenous injections of gentian violet, which has apparently selective action against gram-positive staphylococci. It does not affect the streptococcus or the colon bacillus. The intravenous injection of gentian violet, 5 mgm, for each kilogram, is immediately followed by a most alarming cyanosis, which is simply due to the dye in the blood, which causes no harm and passes off in a few hours. Otherwise, practically no reaction results. The authors have administered 8 mgm. for each kilogram of body weight in 0.5 per cent. solution without harm. The pulse may get quite slow and the blood pressure drop. In very feeble patients, cardiac stimulants should be administered. In very weak patients, the injection may best be given in two or three portions intravenously one hour apart, in order to give large doses.

The authors conclude that when blood cultures show a generalized septicemia, mercurochrome and gentian violet can now be offered with the hope of preventing an otherwise fatal ending.

David T. Smith and Horton Casparis[4] report a case of staphylococcus aureus septicemia in an apparently moribund infant, aged fifteen months, that recovered after it was given three injections of a 0.25 per cent. aqueous solution of gentian violet at 24 hour intervals. The first dose was 5 mgm. for each kilogram of body weight. The white blood cell count, which was 22,000 at the time of injection, was reduced to 10,000 twelve hours later, but returned almost to the original count during the next twelve hours. Because of the possibility that the reduction in the white blood cell count was due to the effect of the dye in that concentration, the amount was reduced, and the second and third doses consisted of 3 mgm. for each kilogram of body weight.

(3) Jour. Amer. Med. Ass'n., Mar. 1, 1924.
(4) Ibid., Dec. 29, 1924.

Acriflavin

Acriflavin Intravenously Ineffectual in Experimental Sepsis. Harvey Spencer[5] finds that the largest dose of acriflavin compatible with life when injected intravenously in white mice does not protect them in any degree from a fatal septicemia when produced by intraperitoneal injections of the pneumococcus.

A single intravenous injection, or multiple injections of the tolerated dose does not lead to an increase in the bactericidal action of the serum when tested against *Staphylecoccus aureus.*

Rivanol

Rivanol. Further experience with rivanol leads to somewhat contradictory results. I. Morgenroth and H. Wreschner[6] find, by experiments with staphylococci in animals, that rivanol is five to ten times as efficient as trypaflavin. I. Morgenroth and R. Schnitzler[7] report that against *streptococcus viridans* a four to eight times stronger solution of rivanol is needed for efficiency than against hemolytic streptococci.

In animal experiments C. Brunner[8] found rivanol efficient for staphylococci, streptococci and anaerobes. He used a 1:400 solution for infiltration antisepsis; for surface antisepsis he employed rivanol powder or gauze, moistened with a 1:200 solution.

Katzenstein and Schultz[9] claim rivanol such an efficient antiseptic in peritonitis, as to enable them to close the abdomen primarily. Klapp, Siebrecht and Ujhelyi[1] found an injection of 5 to 10 c.c. of a 1:1000 solution of rivanol especially satisfactory in the treatment of empyema of the joints (knee, wrist, ankle). Haertel and v. Kishalmy[2] report successful healing of abscesses

(5) Jour. Lab. and Clin. Med., February, 1924.
(6) Deutsche Med. Wochenschr., Oct. 19, 1923.
(7) Zeitschr. f. Hygiene u. Infectionskrank., v. 97, 1922.
(8) Klin. Wochenschr., Aug. 20, 1923.
(9) Ibid., Jan. 8, 1923.
(1) Ibid.
(2) Ibid.

of any kind in soft tissues by injection of rivanol without incision. Pain was controlled permanently, the contents of the abscess were sterilized and very slight scar formation resulted. Irrigation of abscesses, previously opened by incision, was not efficient, neither was treatment of pleural empyema by this method. A. Ritter[3] reports favorable results with rivanol in fresh (eight to twelve hour) wounds; about two-thirds of the cases healed by first intention, one third by secondary suture even though slides, taken previously, showed staphylococci, streptococci, or diplococci in many of the cases. Rivanol was not satisfactory in mixed infection. In anaerobic gas bacillus infection it is unreliable. While C. Brunner and A. Ritter[4] report favorable results in animal experiments in surface antisepsis with a 0.5 to 1 per cent. solution and in infiltration antisepsis with a 1:400 solution of rivanol, they found a solution 1:1000 without efficiency on a fresh (one hour) wound. In a clinical case, in which such a solution was used, gas phlegmon set in and made amputation of the thigh necessary. A 1:1000 solution is evidently too weak. Clinical experiments with 1:400 solution also gave bad results, as the injury of the tissues by rivanol seemed to invite infection. [Evidently the problem of "depth antisepsis" has not yet been solved.—Ed.]

QUININ

Mode of Action of Quinin in Malaria. In the opinion of W. Yorke and J. W. S. Macfie[5] quinin destroys directly, or more probably indirectly a certain number, but not all of the parasites, thus liberating antigen which provokes by stimulation of the the host's tissues,

(3) Klin. Wochenschr., Jan. 8, 1923.
(4) Ibid., July 16, 1923.
(5) Jour. Amer. Med. Ass'n., Aug. 30, 1924.

the formation of immune body. If this is formed in sufficient amount, it destroys the remaining parasites. If, for any reason not enough parasites are destroyed to produce sufficient antigen, or if the host is incapable of responding by production of sufficient antibody the infection will not be destroyed and a relapse occur.

EMETIN

Emetin Bismuth Iodid in Amebic Infection. George A. Dowling[6] concludes on the basis of observations of 30 cases that emetin bismuth iodid by mouth is to be preferred to ipecac by mouth and to emetin hydrochlorid hypodermically, as a specific in infection with *Endameba histolytica.*

"A composite history of these patients would give the picture of a patient in middle life, a chronic sufferer from vague and variable abdominal and gastrointestinal troubles; indigestion, gas in the stomach and bowels, flatulence, cramps, dull aches and tender colon; repeated attacks of diarrhea with intensification of all symptoms; occasional blood and pus with diarrheal stools; chilliness, fever and sweats; often constipation between acute attacks; and sometimes rectal pains and cramps; as secondary symptoms intimately or remotely related to the colitis, a marked degree of neurasthenia; at times loss of weight, back pains, leg and joints pains, hemorrhoids and pains at the tip of the coccyx, recurring ischiorectal abscess, pruritus ani, and bad taste in the mouth, nausea and vomiting; and finally and prominently, a general run down condition and *E. histolytica* in the stools."

No attempt was made at treating any patient without placing him at rest in a hospital. Dowling has discarded ipecac by mouth and the hypodermic administration of emetin for the following reasons: (1) the hypodermic

(6) Jour. Amer. Med. Ass'n., Nov. 17, 1923.

administration of emetin hydrochlorid is quite painful; (2) five patients developed a sensory neuritis of such a degree that complaint was bitter for a long time, and complete relief from pain was not secured for three months in one case; (3) at least one patient with myocarditis already present had his heart symptoms made markedly worse, apparently from the toxic effects of the drug; (4) failure to clear the stools of the amebas occurred in one patient whose treatment was very carefully repeated and carried out; other failures were caused by the refusal of the patient to continue a treatment considered by him unduly punishing; (5) it is admitted that more than one course of this treatment is usually necessary.

Since he changed to the emetin bismuth iodid treatment by mouth, no failures have been encountered, either by reason of the patient's refusal or inability to continue the treatment, or through failure to remove the amebas completely from the stool. He therefore recommends the following routine: a daily dose of 0.2 gm. in a lightly coated keratinized capsule given by mouth at 5 a. m. each day until a total of 2.2 gm. has been given. Each dose should be preceded by morphin sulphate or pantopon hypodermically, and the regular routine as to food and quiet observed. Sometimes nausea and depression caused treatment to be suspended for a day. After the twelve days of treatment, the patients required about two days before getting on their feet.

ANTISCABIOSA

Sulphur

A 24 Hour Treatment of Scabies. Arthur M. Greenwood[7] speaks highly of the treatment described in 1920 by Svend Lomholt of Copenhagen. The directions for

(7) Jour. Amer. Med. Ass'n., Feb. 9, 1924.

the preparation of the ointment which must be carefully followed are:

"1. One kilogram of sublimed sulphur is mixed with 2 kg. of 50 per cent. solution of potassium hydroxid (as free from water as can be obtained). Gentle heat is applied until reaction ceases and the solution becomes clear. When the process is complete, one should be sure that the sulphur is in excess to a slight degree.

"2. Petrolatum, 225 gm., is mixed with wool fat, 225 gm., without heat.

"3. To this mixture is added 375 gm. of the solution of sulphur and potash mentioned above.

"4. To 40 gm. of 20 per cent. sodium hydroxid solution is added 28 gm. of zinc sulphate. The mixture is agitated thoroughly until reaction ceases, poured on filter paper, and washed thoroughly; then the washed precipitate is added to the foregoing.

"5. Liquid petrolatum is added to obtain a total weight of 1,000 gm.

"6. Five grams of oil of bitter almond is added to check the somewhat disagreeable odor of hydrogen sulphid."

The important elements in the ointment are the sulphids of potassium, on which its activity depends, a production of hydrogen sulphide taking place when the ointment is placed on the skin.

The directions for use of the ointment are as follows. The patient receives an ordinary cleansing bath, dries himself thoroughly, and afterwards rubs the whole of his body, except his head, carefully with the ointment. The ointment must cover all the skin, but hard rubbing is neither required nor desirable. The patient ought then to wait for a quarter of an hour to give the ointment time to get into the skin; after this he can go to bed. The next day, at about the same hour, he receives a bath and fresh underclothing, and the treatment is finished. Meanwhile, all his clothes and bedding have been disinfected.

The author has used it in 84 cases with three failures in cases in which the patient did not follow directions. In two cases dermatitis followed its continuous use for five days.

Treatment of scabies would be more successful if every case could be treated in the hospital ward; it is commonly necessary to treat the entire family. It is because of these circumstances that the 24 hour method of treatment is of such value.

ANTHELMINTICS

Carbon Tetrachlorid

Carbon Tetrachlorid, Pharmacology and Therapeutics. R. N. Chopra and J. Borland McVail,[8] in charge of Hookworm Research, Calcutta School of Tropical Medicine, conclude that carbon tetrachlorid is the most efficient anthelmintic known for hookworm. It is of little value in Ascaris infections and of no value against Tenia. The toxic dose of 1 to 4 c.c. for each kilogram of body weight in their experiments is far in excess of the therapeutic total dose of 5 c.c., *i.e.*, 0.13 c.c. for each kilogram which is given as an anthelmintic to a normal individual weighing 65 kilograms. Owing to its low solubility and volatility and consequently slow rate of diffusion, only small quantities are absorbed into the circulation. Large quantities can therefore be introduced into the alimentary canal without untoward effect. When given in medicinal doses and with a purge to persons organically sound it is safe, provided that the drug is pure and that it is swallowed and does not enter the larynx. Carbon tetrachlorid itself and its vapour are very irritating and if brought into contact with the mucous membrane of the respiratory tract in any concentration may produce a

(8) Indian Med. Gaz., October, 1923.

reflex stoppage of respiration and later a stoppage of the heart and death. Therefore *it must not be forced on struggling children.* Large and toxic doses of this drug, whether single or divided, have a damaging effect on the liver parenchyma. With therapeutic doses the damage, if any, is temporary and unimportant. *The great contraindication therefore, is a liver with impaired function such as is caused by alcoholism, chronic or acute.* The liver appears to retain a large proportion of the small quantity which is absorbed and so protects the vital organs from injury. The presence of heavy round-worm infections may also be a contraindication. The action of the drug on voluntary and involuntary muscle is depressant. In medicinal doses it is slightly laxative and it has no abortifacient tendencies.

Carbon Tetrachlorid in Magnesium Sulphate Solution. In view of a paper by Macht,[9] in which it was shown that the systemic action of a drug is delayed or nullified when administered in magnesium sulphate solution because a contrary current is set up in the intestinal wall preventing or delaying absorption, the administration of the two drugs simultaneously was undertaken in field work in Fiji. The results are reported by S. M. Lambert, director of the board's work, as follows:

"In routine work, from 50 to 60 minims of tetrachlorid in 1½ ounces of magnesium sulphate solution is given to adults, according to the size of the individual. Children are given from 3 to 4 minims to the year according to size in appropriate doses of magnesium sulphate. With this method, there have been no reports of headache, a symptom that was not uncommon when the drug was administered alone and followed by the purge. No patients have entered the hospital subsequent to administration of the drug, although hospital treatment is free. Seven thousand persons have been thus treated in the field where dysentery

(9) Jour. Amer. Med. Ass'n., Nov. 3, 1923.

and typhoid fever are not rare. A few persons reported purging for several days, and there is a certain amount of vomiting soon after the dose is given. Security is increased if the carbon tetrachlorid is given with the magnesium sulphate, as both are rejected if there is vomiting." Carbon tetrachlorid was also effective against ancylostomes as well as necators.

The report concludes that carbon tetrachlorid in proper dosage in saturated solution of magnesium sulphate is a safe, reliable anthelmintic for both kinds of hookworm, and that few and minor symptoms result.

Carbon Tetrachlorid Poisoning. B. M. Phelps and C. H. Hu[1] report two fatal cases of carbon tetrachlorid poisoning and a series of animal experiments that tend to confirm the view that carbon tetrachlorid causes central necrosis of the liver, and to suggest that the same drug may cause necrosis of the suprarenal cells.

Case 1 was that of a well nourished negress, aged five and one-half years, who died two days after 1c.c. of carbon tetrachlorid.

Case 2, a man, aged 46 years, died 40 hours after the administration of 3 c.c. carbon tetrachlorid.

In both cases the chief pathologic finding was contral necrosis of the liver. In one case, the suprarenal glands showed necrosis of the cortical cells. The suprarenal glands in the other case were not preserved.

Experiments on guinea-pigs likewise showed that the two organs affected by carbon tetrachlorid, are the liver and the suprarenal glands. The rapidity with which the liver cells around the necrotic areas regenerate, is very striking. Even when the lesion is extensive, it may be completely regenerated at the end of the eighth day.

Effect of Carbon Tetrachlorid Upon the Liver. J. F. Docherty and Lucius Nicholls[2] treated a number of condemned prisoners with 4 c.c. doses of the drug fol-

(1) Jour. Amer. Med. Ass'n., Apr. 19, 1924.
(2) British Med. Jour., Oct. 27, 1923.

lowed in two hours by 60 c.c. of saturated solution of Epsom Salt. Post-mortem examinations were made on three of the prioners. As a result of these studies they conclude that *a dose of 4 c.c. of carbon tetrachlorid may produce fatty degeneration of the liver.* However, these changes in the liver are of a temporary nature and do not appear to contraindicate the use of the drug, because many patients have been treated with much larger doses and have not complained of any discomfort other than very slight giddiness, nor have symptoms or signs of ill health arisen. Consequently it appears that much fat (presumably derived from fatty degeneration) may appear in the liver and yet be a matter of small importance as concerns the health of the patient.

Factors Influencing the Toxicity of Carbon Tetrachlorid. P. D. Lamson, G. H. Gardner, R. K. Gustavson, E. D. Marie, A. J. McLean and W. S. Wells[3] have shown that in dogs carbon tetrachlorid is almost harmless when given by mouth in single doses even up to stomach capacity. This is due to the failure of the drug to be absorbed from the intestine; for, if it is introduced to the tissues directly, symptoms of severe intoxication are readily produced. This happens likewise after inhalation of the drug. If it reaches the portal circulation, there is great depression, vomiting, diarrhea, jaundice, bilirubinemia and bilirubinuria. The liver functions are profundly depressed, and chronic poisoning can readily be induced. Such conditions, though rarely found after ordinary oral administration of carbon tetrachlorid, can be induced if solvents for the drug are administered before or along with it. For practical purposes, alcohol and fats alone come into consideration here. Through the solvent action of these readily absorbed substances, the drug can apparently be passed through the ailmentary barrier that is ordinarily impervious to it. Hence, it

(3) Jour. Pharmacol. and Exper. Therap., November, 1923.

appears more than doubtful whether milk should be used as a vehicle for carbon tetrachlorid, as is sometimes recommended. Fats and alcohol should always be excluded.

RESTORATIVES

ADSORBENTS

Animal Charcoal in Meteorism. L. Pokorny[4] finds that animal charcoal is useful to overcome the difficulties produced by meteorism in gastro-intestinal and kidney roentgenologic examinations. He administers either purified animal charcoal or, for the best effect, Aristo-carbon in tablespoonful doses in one-half glass water three to four times daily two hours before meals. As the procedure failed in aerophagia, the author assumes that the adsorptive action must affect the gas producing factor. [Such dosage might also be of therapeutic value in meteorism.—Ed.]

ACIDS

Hydrochloric Acid in Prevention and Treatment of Diarrhea in Fever. Demuth[5] reports that by adding to 100 c.c. of the undiluted milk 10 drops of the dilute hydrochloric acid, diarrhea and vomiting were prevented or arrested in feverish infants regardless of the origin of the fever (rhinopharyngitis, pneumonia, infected eczema, pyelitis).

Ammonium Acid Phosphate in Tetany. P. György[6] reports twelve cases of tetany most of which were relieved, generally within 24 hours, by doses of from 6 to 20 gm. of ammonium acid phosphate. In some of

(4) Fortsch, a. d. Geb. d. Röntgenstr., p. 192, 1923.
(5) Klin. Wochenschr., May 27, 1924.
(6) Ibid., June 17, 1924.

these cases the administration of the remedy was interfered with by the appearance of symptoms of dyspepsia or of diarrhea. These unfavorable symptoms make it sometimes necessary to discontinue this otherwise very satisfactory and rather pleasantly tasting remedy.

As a result of determination of serum calcium the author arrives at the conclusion that tetany is a problem of calcium-ionization, and that tetany may be relieved without an increase in the total serum calcium, providing its ionization is increased, and for this purpose acidotic treatment is required.

ANTACIDS

Tertiary Phosphates as Antacids in Peptic Ulcer. Howard F. Shattuck, Edward L. Rohdenburg and Lela E. Booher[7] call attention to the fact that Hardt and Rivers (1923) presented patients showing toxic manifestations during the alkaline treatment for peptic ulcer according to the Sippy plan.

The symptoms most often noticed are headache, aversion to food, dry mouth, excessive thirst, lassitude, nausea and sometimes vomiting. With some patients these symptoms appear soon after beginning the alkalis, with others later on. At times they pass away in a few days even though the alkalis are continued in the same amounts. In others again, the toxic symptoms become so pronounced and persistent that the alkalis have to be stopped for a few days, and sometimes the symptoms return as soon as the alkalis are resumed, so that they have to be abandoned at least in quantities sufficient to continuously neutralize the free hydrochloric acid.

Patients showing these symptoms constitute only a comparatively small number of the total number of cases treated. But for ulcer patients developing toxic symptoms and for all ulcer patients with renal disease,

(7) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

some other means of controlling the acidity of the gastric secretion is distinctly needed, to avoid the unfavorable results that may come from the use of the alkalis ordinarily employed.

Greenwald (1923) suggested the possibility of using the tertiary phosphates of calcium and magnesium as gastric antacids, as these do not act as systemic alkalis. More recently, Kantor (1923) showed the marked depressing effect of these salts on the free acid of the gastric juice.

The approximate neutralizing power for hydrochloric acid of the different antacids and alkalis that are being used, kindly worked out by Dr. John A. Killian is shown in Table I.

TABLE 1.—*Neutralizing Power of Antacids and Alkalis*

			HCl Neutralized		Time Required for Neutralization
Salt	Mol. Weight	Grams Used	C.c. of 0.5 N HCl	Gm. HCl	in Minutes
Magnesium phosphate.	335.1	0.5	12.2	0.402	120
Calcium phosphate ...	310.3	0.5	2.9	0.104	15
Sodium bicarbonate...	84.0	0.5	12.5	0.454	2
Calcium carbonate....	100.0	0.5	21.5	0.782	20
Magnesium oxid, heavy	40.3	0.5	45.6	0.829	135

Temperature, 25 C.; indicator, dimethylamino-azobenzene.

It will be noticed that tertiary magnesium phosphate neutralizes approximately the same amount of hydrochloric acid as sodium bicarbonate, while tertiary calcium phosphate neutralizes only about one-fourth as much hydrochloric acid as sodium bicarbonate. It is observed also that calcium phosphate completes its neutralization in about fifteen minutes, while magnesium phosphate takes about two hours. A combination of these two antacids, therefore, gives a relatively rapid neutralizing effect combined with a more slowly acting one, though it has less neutralizing power than the present commonly used combinations of sodium bicarbonate, calcium carbonate and magnesium oxid.

The phosphates were tried in place of the alkalis with cases of peptic ulcer in which the Sippy treatment was being given. In practically every instance the free hydrochloric acid could be controlled with sufficient amounts of the phosphates. The amounts required varied from the equivalent of about 0.65 gm. each of magnesium phosphate and calcium phosphate every hour, to 1.6 gm. of each every hour, the average being about 1 gm. of each every hour. In all cases the urine remained acid. Thus far, no toxic symptoms have appeared even when phosphates were increased to 2.6 gm. of each every hour.

For the most part, the phosphates gave the same symptomatic relief as the alkalis to ulcer patients although in some instances they did not. When they did not give complete relief, alkalis were given for short periods, and later on the phosphates were resumed with satisfactory results. Time alone will show whether the phosphates are as effective as the alkalis in promoting the healing of the ulcer. Perhaps, it will develop, with greater experience, that the alkalis now commonly used should continue to be used in the usual case, the phosphates being reserved for those patients showing toxic symptoms, alkalosis, etc., with the alkalis, and for ulcer patients with damaged liver or kidneys.

HEMOSTATICS

Sodium Citrate as a Hemostatic. N. Rosenthal and G. Baehr[8] call attention to the fact that sodium citrate shortens the blood coagulation time. When sodium citrate is administered intravenously in fairly large doses (0.5 gm. for dog or cat, from 3.0 to 8.0 gm. for man), it produces a pronounced and progressive shortening in the coagulation time of the blood, which

(8) Archiv. Intern. Med., May, 1921.

usually reaches its maximum within one hour and may persist for many hours. A slow return to the normal occurs within 24 hours. This action of sodium citrate on the coagulation of the blood *in vivo*, exactly opposite to that occurring *in vitro*, they believe it to be dependent on some effect on the blood platelets. While these are not directly destroyed by the citrate, they are damaged by contact with it and are then destroyed by the spleen or other organs and their thromboplastic contents gradually liberated. Slow intravenous injection of large doses of sodium citrate up to 5 gm. has been successfully employed in arresting hemorrhages due to gastric ulcer, typhoid fever, pulmonary tuberculosis and other hemorrhagic conditions that are not accompanied by diminution or disease of the blood platelets. Too hasty an injection is dangerous. In hemorrhagic diseases in which there is a deficiency in the blood platelets, its use is strictly contraindicated as it may cause an increase in the hemorrhagic tendency.

M. Renaud[9] also reports almost immediate arrest of profuse hemorrhages by intravenous injection of from 10 to 30 c.c. of a 30 per cent. solution of sodium citrate in 21 cases of uterine cancer, while no effect was obtained in three cancer cases with anemia of the pernicious type. Tuberculous hemoptysis was also arrested promptly and permanently by this means. The author regards sodium citrate as the most reliable hemostatic at our command at present.

Control of Epistaxis. Joseph G. Levine[1] uses in obstinate nasal hemorrhage an ordinary rubber finger cot about the size of the index finger or smaller, covered with a bland lubricating jelly, grasped with the nasal forceps, and inserted into the bleeding nasal cavity, the blind pouch end foremost, as far as it will go, with the open end just protruding from the nasal

(9) Bull. Soc. mèd. des hôp. de Par., May 16, 1924.
(1) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

orifice. A one-half inch strip of plain gauze is then packed into the rubber incasement as firmly as possible with the nasal forceps, while the finger cot is held from sliding in.

The bleeding is effectively controlled, because the gauze packing cannot become blood soaked and loosen, while the elasticity of the distended finger cot distributes the force of the pressure evenly in all directions. It is not necessary to remove this packing within 24 hours, because the protection afforded by the rubber cot to the gauze prevents it from soaking up sapremic exudates and blood that often promote further hemorrhage. The removal of the packing is simple and not discomforting. One first removes the gauze and then slides out the finger cot.

Robert Sonnenschein[2] suggests filling the finger cot with cotton.

Raymond Johnson lubricates a condom with petrolatum, and inserting a nasal applicator, pushes it back through the nasal aperture, then removes the applicator, and inflates the condom with the bulb of a Tycos sphygmomanometer or by mouth to the desired pressure, having an assistant or one of the family tie it off close to the nasal aperture. Removal of the condom is simple by puncturing it with a needle or any sharp instrument and slipping it out. This method works well with nervous children, as it takes only a minute to do it.

J. B. H. Waring places two or more Bernay's sponge splints inside the previously lubricated finger cot, which is then introduced with nasal dressing forceps, or with the fingers if forceps are not at hand, into the nasal orifice from which comes the hemorrhage. A drop or two of hydrogen peroxid or sterile water on the ends of the splints causes them to expand rapidly, filling the nasal passage with a firm even, pressure, which will not only quickly stop bleeding in Kiesselbach's area, but farther back and upward, if needed.

(2) Jour. Amer. Med. Ass'n., Feb. 2, 1924.

It is needless to say that any dressing which interferes with nasal aeration and drainage to a greater or less extent should be removed just as soon as it is safe to do so, as otherwise sinus or aural complication may be set up by this blockage of nasal ventilation and drainage.

[Touching the bleeding spot with a crystal of silver nitrate is the best method when it is as accessible, as it most commonly is—on the septum, right near the opening of the nares—Ed.]

Anaphylaxis Following Organic Hemostatics. Bernard E. Sayre[3] reports a case of severe anaphylaxis following application of coagulose (which is concentrated horse serum in powder form) applied to the bleeding surface. The patient had been operated on for a severely toxic goiter, was not sensitive to horses nor subject to asthmatic attacks. About fifteen minutes following the application of the blood coagulant, the patient suddenly became cyanotic, breathing with difficulty and inspiring in short gasps. Foam appeared at the mouth. Within a minute or so, breathing ceased. The heart became rapid and the pulse somewhat weak, but continued to beat regularly. Artificial respiration was resorted to, stimulants were given hypodermically, oxygen was administered, and breathing was finally resumed. Cyanosis lasted for ten minutes.

J. B. DeLee[4] reports a case of fatal anaphylaxis following injection of 4 c. c. of Hemoplastin (Parke, Davis & Co.) against persistent postpartum hemorrhage. Within one and one-half minutes the patient collapsed, became extremely pale; she said she could not get her breath, and feared she would die; then she expired. There was no pulse at the wrist, epinephrin was administered at once, and again, ten or twelve minutes later, intracardially, with no response. Artificial respiration was continued one hour. The patient was a sufferer from asthma and her attacks were elicited by the mere

(3) Jour. Amer. Med. Ass'n., Jan. 3, 1925.
(4) Ibid., May 10, 1924.

approach of a horse. Dr. DeLee learned since this accident of another case wherein death occurred a few minutes after the administration of hemoplastin to a woman sensitized by the previous injection of horse serum.

In view of these reports, Ludvig Hektoen[5] examined specimens of the various coagulants available to determine whether or not they contained material which might produce such reactions. He found that Coagulen-Ciba, Fibrogen-Merrell, Hemagulen-Lilly, Kephalin-Armour, Hemostatic Serum Lapenta, Thromboplastin-Lederle, Thromboplastin-Squibb, Thromboplastin Hypodermic-Squibb, Thromboplastin Solution-Armour, Precipitated Horse Serum (Coagulose)—P. D. & Co. all contained animal protein, in most instances horse or beef proteins. Hence, *physicians should be warned against their use in any case in which there is a hypersensitivity to such substances.* Hypersensitivity to horse proteins is not at all an infrequent condition. By preliminary administration of small doses, it could be easily determined whether or not a reaction would occur.

HEMATINICS

Iron Stimulates the Formation of Red Blood Corpuscles. When an emulsion of red blood corpuscles saturated with oxygen is kept for several hours in an incubator in a sterile manner and protected against air, the oxyhemoglobin is not reduced. In certain anemias, such as that following hemorrhage in pernicious anemia and of carcinoma, reduction occurs. Evidently we have here an indication of regeneration of red blood corpuscles.

M. J. Roessingh[6] used this method to study upon patients the effect of iron in anemia. He found that

(5) Jour. Amer. Med. Ass'n., Aug. 30, 1924.
(6) Klin. Wochenschr., Apr. 15, 1924.

after the use of iron there was quite uniformly an increase in the oxygen consumption of the blood cells, which he takes as an indication of increased blood formation.

Uselessness of Germanium Dioxid in Secondary Anemia. J. D. Garvin[7] reports a series of nineteen cases of anemia associated with chronic infectious arthritis, chronic glomerulonephritis, and chronic sepsis in which germanium dioxid given hypodermically in doses of from 12 to 20 mgm.; or by mouth in doses of 10 to 100 mgm., every one to four days, over periods ranging from one to five weeks, produced practically no increase in the number of erythrocytes, nor any appreciable rise in the hemoglobin content of the blood.

ALTERATIVES

Iodid

Iodids in Goiter. In the middle of the last century Chatin observed that the incidence of endemic goiter and cretinism were highest in districts where the iodin content of the food and water was low. He expressed the opinion that both endemic goiter and cretinism could be prevented by the continued administration of small quantities of iodin. More recent investigations have confirmed and extended these observations of Chatin.

As the administration of iodin is not equally beneficial in all forms of goiter, and in some may be actually harmful, it is important that the type of goiter present be determined as accurately as possible before beginning treatment.

The benign diffuse enlargement is known as simple, colloid, diffuse colloid, or endemic goiter. The diffuse enlargement of the toxic type which is always associated with some degree of exophthalmos and with symptoms similar to those produced by the artificial administra-

(7) Minn. Med., June, 1924.

tion of thyroxin is known as exophthalmic goiter or Graves' disease. Nodular enlargements due to single or multiple adenomas within the thyroid gland being more common where diffuse colloid goiter is prevalent, is also an endemic form of goiter. Palpable nodular enlargements are rarely found before the age of twenty, and during the third decade seldom produces symptoms. Later, however, symptoms similar to those found in exophthalmic goiter, but without the presence of exophthalmos, may develop. At this stage the condition is called toxic adenoma of the thyroid.

Diffuse colloid goiter, the common endemic form, usually appears first at puberty and is commonly referred to as adolescent goiter. In females it shows a periodic increase in size at the time of menstruation and during pregnancy. The prevention of this form of goiter, both in man and animals, by the administration of small quantities of iodin has been definitely proved by Marine (1917). This observer has also shown that congenital goiter and cretinism can be prevented by the administration of iodin to the mother during pregnancy. In view of this it is the duty of every physician to be on the look out for the development of diffuse colloid goiter. In the later stage of the disease iodin is not nearly so effective in treatment, and in cases over 25 years of age may stimulate a latent adenoma to the development of toxic symptoms.

Both types of toxic goiter—exophthalmic and toxic adenoma—tend to occur more frequently in cases giving a history of earlier thyroid enlargement. For this reason the use of iodin for the treatment and prevention of adolescent goiter is of additional importance. As already mentioned, nodular goiters tend to become active after the age of 40, and are the most common cause of toxic goiter after 50 years of age. Exophthalmic goiter, on the other hand, develops earlier, more rapidly incapacitates the patient than toxic adenoma, and is the most common form of toxic goiter before 40 years of age. In

both exophthalmic goiter and toxic adenoma, tachycardia is present and the basal metabolism is above normal, indicating increased activity of the thyroid gland. The ideal treatment for both conditions is the removal by operation.

Iodid in Exophthalmic Goiter. It is noted in the Journal of the American Medical Association (Oct. 18, 1924), that the first recorded use of iodin in exophthalmic goiter is due to a fortunate therapeutic error by Trousseau who in 1863 prescribed for a woman suffering from subacute exophthalmic goiter, with a heart beat of 140 to 150 tincture of iodin instead of tincture of digitalis as he had intended. After the patient had taken from 15 to 20 drops of tincture of iodin a day for a fortnight, she came back her pulse being only 90. Trousseau having discovered his mistake, substituted tincture of digitalis for that of iodin; but, after another fortnight, the pulse had again gone up to 150, so that he at once returned to the iodin.

Henry S. Plummer and Walter M. Boothby[8] intentionally repeated Trousseau's "error" and report 600 patients, having exophthalmic goiter, so far treated with Lugol's solution at the Mayo Clinic. Approximately two-thirds of the patients with exophthalmic goiter were greatly benefited; one-fourth slightly benefited; the remainder, or about one patient in twenty, was not benefited. The probability of the iodin doing harm is less than 1 in 600. The mortality rate following surgical procedures for exophthalmic goiter has been reduced at the Mayo Clinic to 1.7 per cent., based on the number of patients operated on, and to less than 1 per cent. when computed on the basis of the number of operations.

Lugol's solution was used as the iodin preparation because it is an aqueous solution of iodin (5 per cent.) and potassium iodid (10 per cent.) and therefore provides a large amount of iodin loosely combined with

(8) Illinois Med. Jour., December, 1924.

potassium. It has been found that 10 drops of Lugol's solution, well diluted with water and followed by half a glass of water is, on the average, the optimal dose. Certain patients have been observed who did not react on 5 drops, but did react on 10 drops. Some of the most rapid reactions have been observed when 10 drops were given three times a day. At the present time the routine dose in the average moderately severe case is 10 drops daily; if there is a marked gastro-intestinal or mental crisis, this amount is given three of four times a day for a few days, and then reduced to once a day. If the drug is not tolerated by mouth, it is given in similar doses by rectum; rectal administration, however, has only been found necessary for a few days for patients who had severe gastrointestinal crisis, and constant nausea and vomiting. As soon as the vomiting was controlled, the solution was given by mouth. *Patients with adenomatous goiter without hyperthyroidism are rendered "hyperthyroid" by the administration of iodin.* Hence these patients must not be given Lugol's solution.

E. H. Mason[9] also finds that cases of exophthalmic goiter, in which abundant iodin is given, lose the toxic state. Metabolism reaches a normal level in one week. The exophthalmos recedes and the thyroid gland becomes smaller. It seems that, in exophthalmic goiter, the thyroid cannot completely iodize the molecule, and this is the cause of the toxicity. Iodin enables the gland to manufacture the normal product. Hence, exophthalmic goiter, may be classed as a dysthyroidism. In atypical cases, with moderate exophthalmos, the toxicity does not completely disappear with iodin treatment. This is a mixed type, partly dysthyroidism, and partly hyperthyroidism. The latter condition persists in spite of iodin therapy. Hyperthyroidism itself must be corrected by thyroidectomy.

These favorable results have also been confirmed by Duncan Graham[1].

(9) Jour. Amer. Med. Ass'n., May 24, 1924.
(1) Canadian Med. Ass'n. Jour., September, 1924.

Before beginning iodin treatment, it is extremely important to determine by palpation of the gland if adenomata are present, for the use of iodin may stimulate a benign adenoma to activity or aggravate the symptoms produced by a toxic adenoma. In addition to regular medical treatment, a case of exophthalmic goiter should receive 10 minims of Lugol's solution daily for a week to ten days. During this short period of iodin treatment the basal metabolism falls toward the normal level, the tachycardia decreases, and the general condition of the patient improves. The diffuse enlargement of the thyroid decreases in size and adenomata not found at the beginning of treatment may now become palpable. If adenomata are present the use of iodin should be discontinued and surgical treatment advised. With cases that have shown satisfactory improvement following preliminary iodin treatment and in which adenomata are not present, medicinal treatment may be continued, giving a smaller daily dose of iodin, usually 1 to 3 minims of Lugol's solution. Should iodin treatment be discontinued later, cases of exophthalmic goiter undergoing this form of treatment must be carefully observed as a sudden relapse may follow the cessation of iodin therapy. In the authors' experience, thyroidectomy following preliminary iodin treatment gives more satisfactory results. If patients are operated upon, iodin treatment as recommended by Plummer, should be continued during the postoperation period to lessen or prevent the danger of a thyroid crisis.

J. Marion Read[2] considers iodin the only medication in this disease that might be regarded in the light of specific therapy.

Since the admonitions of Kocher against giving iodin in so-called hyperthyroidism, physicians have been fearful lest the hyperactive gland be whipped up to still greater activity by this element. This is one of the unfortunate results of accepting an unproved theory of

(2) Jour. Amer. Med. Ass'n. Dec. 20, 1924.

causation as a basis of therapy. Iodin in various forms has been used in times past and advocated by a few courageous physicians, with varying degrees of success. With the growing tendency to view this disease as representing probably a qualitative change in the thyroid secretion, the giving of iodin has become more popular.

Read believes that results equally beneficial to those obtained at the Mayo Clinic in pre- and postoperative care may be obtained with iodin in the nonsurgical treatment of exophthalmic goiter. The response varies in different individuls and a few do not tolerate it, while others show marked improvement. The beneficial results will be manifested by early abatement of those symptoms which may be interpreted as due to toxema. Decrease the pulse rate is usually the first objective sign. Subsidence of tremor and a subjective feeling of well being are often noted, together with a drop in the basal metabolic rate. Compound solution of iodin is recommended by the Mayo workers. Potassium iodid may also be used. If compound solution of iodin is used, from 3 to 5 drops a day should be the initial dose to test the indivual's tolerance. This may then be increased to from 10 to 12 drops daily.

Remedying Iodid Deficiency. J. F. McClendon and Joseph C. Hathaway[3] advocate that iodin should be added up to 1 part per hundred million in goitrous regions. This is easily accomplished by adding about one-tenth pound (45 gm.) of sodium iodid for each million gallons of water. The iodin content would then be less, in fact only from one-fifth to one-tenth of the iodin content of drinking water of some of the cities of the United States. Assuming a person drank a liter a day of the treated water, that would give him 0.01 mgm. of iodin a day and by this the iodin requirements of the individual would be satisfied. The water supplies of Rochester, N. Y., and Sault Ste. Marie, Mich., are now being treated with sodium iodid.

(3) Jour. Amer. Med. Ass'n., May 24, 1924.

M. Olin[4] believes that the best method of overcoming iodin deficiency and preventing goiter would be a law requiring that *all salt sold for human and animal consumption in goitrous areas contain sufficient iodin* (1 *part per* 5000) *so that the minimum requirements of* 300 *mg. a year, would be normally taken in by every one in the area.*

This method is open to fewer objections than any of the other methods, as it is a natural way of correcting an environmental deficiency of iodin content in the natural food supply, and will furnish no greater amount of iodin than is supplied naturally in communities which do not have a goiter problem owing to the fact that they have ample iodin in the soil and water. This procedure is in line with many other tendencies in the field of nutrition, away from over-refinement which eliminates much of the food value. Crude salt almost universally contains some iodids, and the statement has been variously made that refinement of the salt is one of the principal contributory causes of the increase of thyroid enlargements in the United States.

Up to date, the most satisfactory method that has been in use is that of giving 10 mgm. of sodium iodid in a chocolate tablet [tastes bad—Ed.] or 10 mgm. of iodin as iodostarine in a chocolate tablet [or sajodin chocolate tablets—Ed.] once a week for 40 weeks to all children in the schools, thus supplying from 300 to 400 mg. of iodin a year.

While results of this method have been very spectacular in the reduction of the percentage of individuals showing thyroid enlargement, and the medical profession in the United States and in Europe is endorsing the procedure, it is open to several adminstrative objections. 1. It does not reach the children early enough in the rural districts. 2. It does not reach the pregnant mother. 3. It must depend on a local interest and knowledge of the subject. 4. There must be constant propaganda in every

(4) Jour. Amer. Med. Ass'n., Apr. 26, 1924.

community to keep the procedure in effect. 5. Persons overtreat themselves with these products. 6. The cost, while very small, will militate against the procedure because it is a specific cost and can be focused on for discussion. 7. Results cannot be made apparent except by resurvey. Obviously, in many instances in which the scheme had once been tried out, it would be dropped from lack of knowledge as to the results obtained.

It has been proposed that iodin be given in municipal water supplies, and tried out at Rochester, N. Y., Saulte Ste. Marie, Mich., and elsewhere. While this method is perfectly possible, it is open to the objection that only an infinitesimal amount of the water, less than 1 per cent., that is pumped by a municipality is used for drinking purposes, and only the municipal population can be reached.

T. Clark[5] recommends the administration of 30 c. c. of syrup of hydriodic acid, or of an equivalent amount of iodin in any other available form, for a period of one month during the first half of pregnancy to protect the mother and fetus against goiter. He considers desiccated thyroid dangerous.

[It is to be hoped that the use of iodized table salt may come into more general use for the prevention of goiter. Iodized salt is now on the market and obtainable through grocers.—Ed.]

Iodin Content of Sea Foods. The Journal of the American Medical Association, Jan. 26, 1924, quotes from a report of the United States Bureau of Fisheries that marine fishes, mollusks and crustaceans are higher in iodin content than any other common foods. The only foods which contain more iodin than oysters, clams and lobsters are the marine algae which, unfortunately, do not enter into the dietary of the majority of Americans. The fact that oysters, clams and lobsters contain about 200 times as much iodin as beef steak or milk, shrimp 100 times as much, crabs and most ocean fishes

(5) Pub. Health Rep., Jan. 18, 1924.

50 times as much should be of considerable importance in the nutrition of people living in the so-called goitrous belts. It is evident that, by replacing meat with marine fish or shell fish in the diet two to three times each week, the amount of iodin ingested can be increased considerably. This is especially important in planning the diet of young girls living in districts where disorders of the thyroid gland are common, as they are particularly susceptible to goiter.

Action of Iodid Upon the Circulation. In view of the favorable effect of iodid in circulatory disturbances, most especially of arteriosclerotic nature, and upon angina pectoris and aortic aneurism so closely connected with arteriosclerosis, even in cases in which there is no syphilitic infection, D. Bloom[6] undertook a careful clinical study of 23 patients who took from 0.5 to 10 gm. of potassium iodid (dissolved in 200 c. c. of water, 1 tablespoonful every 2 hours) within 48 hours. In more than half of the cases a reduction of systolic blood pressure and an increase in pulse volume as determined by Sahli's volumebolometer were noted, as well as an increase in pulse frequency. This shows clearly that potassium iodid acts upon the circulation. The fact that it increases the pulse volume shows that it improves the heart's action. The lowering of the blood pressure can only be due to dilation of blood vessels as changes in viscosity can not be determined according to more recent investigations. These observations explain the favorable effect of this remedy upon various circulatory disturbances, most especially arteriosclerosis, for it increases the blood supply to the various organs and not only improves the heart's action in this manner but also lessens the resistance it must overcome.

Calcium

Calcium in Nephritic Edema. In 1911, Meyer and Cohn found that a certain amount of calcium chlorid

(6) Schweizer. Med. Wochenschr., May 15, 1924.

added to the food of infants caused a decrease in weight, due to loss of water. They stressed the importance of using a comparatively large amount of calcium chlorid if loss of water was to be produced. On the basis of these observations, Schultz, in 1918, gave doses of 10 gm. of calcium chlorid daily to patients suffering from war nephritis, and in several cases prompt diuresis and disappearance of edema occurred. In 1922, Blum reported like results in similar cases, but he found also that with the disappearance of the edema there was a large output of sodium in the urine. As it is known that sodium salts cause retention of fluid in the body, this finding convinced him that sodium was the important substance in the causation of edema and must necessarily be eliminated with the subsidence of the edema.

Norman M. Keith, Charles W. Barrier and Mary Whelan[7] report two carefully studied cases of nephritis with edema, one of whom had resisted other modes of treatment in which calcium chlorid (10 gm. daily) caused diuresis and loss of edema. As a study of inorganic ions during the diuresis shows a positive balance of calcium and a negative balance of chlorin and sodium, they conclude that when calcium chlorid is ingested, calcium is eliminated by the bowel, and chlorid by the kidney. With this, sodium may be discharged in large amounts and water made available for elimination.

Rockwood and Barrier[8] also confirm the results obtained by Schultz and Blum in the treatment of nephritis and nephrosis, and further demonstrate that calcium chlorid is efficacious in many cases in which calcium lactate fails to produce diuresis. This suggests that the action of calcium as diuretic, in cases of nephritis with edema, may be due in part to a change in the acid-base equilibrium of the body, causing the tissues to liberate water for excretion by the kidney, or causing a change in the damaged kidney so as to

(7) Jour. Amer. Med. Ass'n., Aug. 30, 1924.
(8) Arch. Int. Med., May, 1924.

permit the excretion of water and salts. That acidosis is however not the only cause for starting diuresis is indicated by the presence of acidosis with oliguria for a considerable period in certain cases reported.

Calcium Administration. W. H. Jansen[9] found that peroral administration of small doses of calcium does not increase the blood calcium content. Large peroral doses of soluble calcium salts, such as 1.0 to 1.5 gm. lead to a transient increase, up to 50 per cent. in the adult, within two to three hours after ingestion and are followed by a decrease to the previous condition or transiently below it. After intravenous administration, the maximal increase was obtained within ten minutes, and this was followed by a gradual decrease to the previous condition. He considers intravenous as well as subcutaneous injection ineffective in adults with normal blood calcium content; but an increase to the normal is obtainable in individuals with subnormal blood calcium content and this can be maintained for some time. The degree of the increase depends upon the salt administered. He considers the organic salt—isobutyrate of calcium (Optochal)—the most suitable for injections because it is easily dissolved, has neutral reaction and no unpleasant by-effects, even in large peroral doses. Calcium butyrate may be administered intravenously in isotonic solution (3.78 per cent.) or in 10 per cent. solution in quantities of 0.08 to 0.17 gm. for each kilogram of body weight.

Intravenous Injections of Calcium Chlorid Do Not Harm the Kidney. As 5 c. c. of a 10 per cent. aqueous solution of calcium chlorid given daily for three days hastens blood coagulation, as evidenced by a lowering of the blood coagulation time and the absence of postoperative hemorrhage in jaundiced patients, John P.

(9) Deutsch. Archiv. f. klin. Med., October, 1924.

Bowler and Waltman Walters[1] undertook experimental work to determine whether intravenous injections of calcium chlorid in the amounts given had an effect on renal function or renal tissue.

By experimental work on seven dogs, in four of which an artificial obstructive jaundice was produced by ligating the common bile duct under anesthesia and with aseptic technic, they arrive at the conclusion that it was not possible to demonstrate a deleterious effect on the kidneys of any of these dogs, either clinically or pathologically.

Calcium Intravenously in Acute Adnexitis. A. v. Fekete[2] reports 28 cases of acute salpingo-oophoritis relieved by intravenous injections of 10 c.c. of a 10 per cent. solution of calcium chlorid every second day. In most of his cases the fever and pains subsided after five or six injections. Excessive menstruation, hemorrhage and leukorrhea were also favorably influenced. The inflammatory hyperleukocytosis was not affected.

Calcium and Parathyroid Gland in Hyperesthetic Rhinitis. Robert Sonnenschein and Samuel J. Pearlman[3] find it doubtful whether the blood calcium content is the only one and essential factor in the causation of hyperesthetic rhinitis, since none of the cases in their series of clear cut instances showed a definite deficiency. While calcium intravenously probably acts as a sedative and gives temporary relief in many cases, its action when given by mouth is undetermined. Ultraviolet ray radiation may be beneficial; further trials are needed to prove this point conclusively. There is little evidence that in man, at least, parathyroid feeding is of any value, or that thyroid has any value in hyperesthetic rhinitis even when used as an adjuvant to calcium or parathyroid.

(1) Jour. Amer. Med. Ass'n., Oct. 18, 1924.
(2) Monatschr. f. Geburtish u. Gynäk., September, 1924.
(3) Jour. Amer. Med. Ass'n., Dec. 20, 1924.

RESUSCITATION

Heart Massage

Cardiac Massage in Syncope. A. S. Levy[4] urges that in anesthesia syncope, heart massage should be commenced within five minutes of the onset of the syncope and performed by the hand in the left pleural cavity, the right ventricle being compressed as well as the left. Sub-diaphragmatic massage is a waste of time. Effective artificial respiration must be maintained throughout. For cardiac massage to be effective, the cardiac poison present must be a volatile one. The main use of cardiac massage is in cases of "chloroform syncope," which is a sudden form of fibrillation of the heart unconnected with overdosage. There is always a chance of spontaneous recovery from this condition within two minutes but after the lapse of this time there is no hope of recovery except by means of cardiac massage.

Artificial Respiration

At the recent meeting of the American Medical Association a symposium on resuscitation was held, from which, on account of the practical importance of the subject, rather extensive quotations are given.[5]

For the treatment of electric shock, drowning, and other conditions producing complete cessation of breathing, the Schäfer manual prone pressure method should be used in preference to any other. The use of artificial respiration apparatus should be discouraged, for the simple manual method is much more effective. There is some evidence that mechanical devices may even be injurious to the lungs. These apparatus have few, if any, well substantiated cases of resuscitation to their credit. On the other hand, hundreds of lives have been saved with the manual method.

(4) British Jour. of Anesth., April, 1924.
(5) Jour. Amer. Med. Ass'n., Sep. 6, 1924.

It is essential that the medical profession should learn the prone pressure method. All employees of electric light companies and telephone companies, all boy scouts, and a large number of the better trained policemen and firemen now know how to administer the prone pressure method. It is sometimes charged against the medical profession that, in cases of drowning and electric shock, in which lives probably could be saved by the immediate and continued application of this most effective method of artificial respiration, lives have been lost because the first physician who reached the case was unacquainted with the method. He has therefore ordered the electric lineman or policeman or boy scout who was administering the prone pressure method effectively, and was well on the way to saving life, to desist. He has then either declared the patient dead or has called an ambulance and sent him to the hospital, where he arrived dead. If there is any basis for this charge, it is time that the medical profession removed it by learning the prone pressure method. Heretofore, a medical man suddenly confronted by a patient in nearly any one of the conditions mentioned has generally confined himself to administering a hypodermic injection. This is the ambulance physician's favorite contribution to resuscitation, the value of which is practically *nil*.

"It is only fair to add also that, in ordinary medical practice, a physician in the past has rarely seen cases requiring artificial respiration. Often he fails to realize that a perfectly healthy young man, whose breathing has been temporarily stopped by an electric shock or by immersion in water, is a very different subject from the patient who stops breathing after a long and wasting, or acute and destructive illness. Often, in the drowning or electric cases, the vital machine merely needs to be started again. It is like cranking an automobile when the engine has stalled and the self-starter is out of order. With the increasing use of electricity,

not only for transportation and industry, but also in our homes, for light, for cooking, and, most dangerous, for the laundry, electric shock has come to be one of the ordinary hazards of modern life, and every one should know how to render first aid. The essentials of artificial respiration are that it should be applied without the loss of a moment, without waiting to telephone or send for apparatus, and that, even if the patient is at first pulseless and apparently dead, it should be continued for three hours, or until spontaneous breathing returns, or rigor mortis develops.

"It has been proved, that the exchange of air which results from the prone pressure method is quite sufficient to maintain life. It more nearly imitates the natural process of breathing than does any other method. It is also the easiest method to perform and the least fatiguing, and it can be performed by one person without assistance."

Wills Maclachlan[6] gives the following detailed directions for resuscitation from electric shock, which merits the greatest possible publicity.

"The victim should be quickly released from the current, care being taken to avoid receiving a shock. Any dry non-conductor (rubber gloves, clothing, wood or rope) may be used to move either the victim or the conductor. Metal or any moist material should not be used. If both the victim's hands are grasping live conductors, an effort should be made to free them one at a time. If necessary, the current should be shut off.

"The nearest switch should be opened, if that is the quickest way to break the circuit.

"If it is necessary to cut a live wire, an ax or a hatchet with a dry wooden handle should be used, the face being turned away to protect it from an electrical flash.

"As soon as the victim is clear of the live conductor, a finger should be put in his mouth and throat to

(6) Jour. Amer. Med. Ass'n., Sep. 6, 1924.

remove any foreign body, such as tobacco or false teeth. If the mouth is tight shut, no attention should be paid to the foregoing instructions until later, but resuscitation should be immediately begun. The patient will breathe through the nose and, after resuscitation has been carried on a short time, the jaws will probably relax and any foreign substance in the mouth can then be removed. No time should be taken to loosen the patient's clothing as every moment of delay is serious.

"The patient should be laid on the abdomen, one arm extended directly overhead, the other arm bent at the elbow, and with the face resting on the hand or the forearm so that the nose and mouth are free for breathing. (Fig. 3.)

"The resuscitator should kneel, straddling the patient's hips, with the knees just below the patient's hip bones or the opening of the trouser's pockets. The palms of the hands should be placed on the small of the back with the fingers resting on the ribs, the little finger just touching the lowest rib, the thumb alongside the fingers, the tips of the fingers just out of sight. (Fig. 3.)

Fig. 3.—Hands in position.

"With arms held straight, the resuscitator should swing forward slowly so that the weight of his body is gradually brought to bear on the subject. (Fig. 4.) This operation, which should take from two to three seconds, must not be violent, as internal organs may be injured.

The lower part of the chest and also the abdomen are thus compressed, and the air is forced out of the lungs; the diaphragm is kept in natural motion; other organs are massaged, and the circulation of the blood is accelerated.

Fig. 4.—Pressure on.

"Now the resuscitator should immediately swing backward so as completely to remove the pressure, thus returning to the position shown in Fig. 5. Through

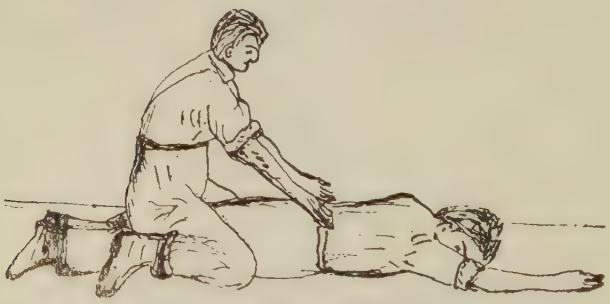


Fig. 5.—Pressure off.

elasticity, the chest wall expands and, the pressure being removed, the diaphragm decends, and the lungs are thus supplied with fresh air.

"After two seconds, the resuscitator should swing forward again. Thus the double movement of compression and release should be deliberately repeated from twelve to fifteen times a minute, a complete respiration

being made in four or five seconds. If a watch or a clock is not visible, the natural rate of the resuscitator's own deep breathing should be followed. The proper rate may be determined by counting—swinging forward with each expiration and backward with each inspiration.

"As soon as this artificial respiration has been started and while it is being continued, an assistant should loosen any tight clothing about the patient's neck, chest and waist. The patient should be kept warm. Ammonia should be placed near the nose, the safe distance being determined by first trying how near it may be held to the resuscitator's own nose. No liquids whatever should be given by mouth until the patient is fully conscious.

"Artificial respiration should be continued without interruption (if necessary for four hours) until natural breathing is restored. Cases are on record of success after three and one-half hours of effort. The ordinary tests for death are not conclusive in cases of electrical shock.

"When the patient revives, he should be kept lying down and not allowed to get up or to be raised under any consideration.

"The patient should then have any other injuries attended to and he should be kept warm, being placed in the most comfortable position.

"Resuscitation should be carried on at the nearest possible point to which the patient received his injuries. He should not be moved from this point until he is breathing normally of his own volition, and then should be moved only in a lying position. Should it be necessary, owing to extreme weather conditions, to move the patient before he is breathing normally, he should be kept in a prone position and placed on a hard surface (door or shutter or the floor of a conveyance), resuscitation being carried on during the time that he is being moved.

"A brief return of spontaneous respiration is not a certain indication for terminating the treatment. Not infrequently, the patient, after a temporary recovery of respiration, stops breathing again. The patient must be watched, and if normal breathing stops, artificial respiration should be resumed at once."

St. Jellinek[7] reports two cases of apparent death from electric shock in one of which artificial respiration, started after ten minutes, resulted in recovery in about an hour; another in which artificial respiration started immediately had to be kept up for three hours before spontaneous respiration appeared. The author concludes that artificial respiration properly carried out and started immediately should be continued long enough. *Only the appearance of post-mortem lividity justifies cessation of effort.*

Carbon Dioxid-Oxygen

Yandell Henderson[8] emphasizes most especially the prevention of respiratory failure in such conditions as carbon monoxid asphyxia, acute intoxication under alcohol and many other volatile poisons, the depression following anesthesia, morphin poisoning, asphyxia of the new-born infant, when respiratory failure is threatening or evidently approaching. There is no need as yet for artificial respiration, for natural breathing still continues, but it is growing weaker. When it stops it will be too late. How are we to effect resuscitation and restoration to normal life?

Inhalation of oxygen alone is not under such conditions a logical procedure. Only in pneumonia must we recognize an exception to this statement. Under nearly all other conditions, oxygen administered for purposes of resuscitation should contain also a sufficient amount of carbon dioxid to stimulate the breathing. Usually, 5 per cent. of carbon dioxid is sufficient in from 90 to

(7) Wien. Klin. Wochenschr, Mar. 1, 1923.
(8) Jour. Amer. Med. Ass'n., Sep. 6, 1924.

95 per cent. of oxygen. It is the use of this mixture administered by a special type of inhaler, the so-called "H. H. inhalator," devised by Henderson and Haggard that has been approved by the last resuscitation commission.

We know now that the stimulant which Nature herself uses to maintain breathing is carbon dioxid. It is the increased production of carbon dioxid during muscular exercise that causes the corresponding increase in the volume of air breathed. If the carbon dioxid in the blood is abnormally decreased by excessive breathing, we know that respiration is liable to stop until the normal amount of carbon dioxid reaccumulates in the blood and again stimulates the respiratory center. Oxygen deficiency, if at all intense, acts as a sort of whip, which excites respiration to activity, and even to excessive activity, but injures at the same time and is liable to be followed by a subsequent period of depressed breathing. Pure oxygen, or air enriched with oxygen, is not a respiratory stimulant. On the contrary, under some conditions it is, in effect, a powerful depressant of breathing. When a man or animal is exposed to a deficiency of oxygen for a time, his breathing is greatly augmented and he blows off more carbon dioxid than the body can well afford to lose from its store of carbonic acid and bicarbonates. If, then, he is suddenly given oxygen, or even merely fresh air, a marked decrease in respiration occurs. The breathing may even stop entirely. It is well known to the men in our city fire departments that a man who has been working in the fumes of a burning building often collapses when he comes out into fresh air. The same effect is known among mine rescue crews. Often, they walk out of the gases in a burning mine with fair vigor and coordination of movement, but fall unconscious after drawing a few breaths of fresh air. In the laboratory, animals that have been kept in a gassing chamber until slightly groggy with carbon monoxid

sometimes collapse when removed into fresh air. Similarly, athletes seldom collapse during a competition, but when the race is over, with its strain on the oxygen-supplying power of lungs and heart, they pant heavily for a few minutes and then collapse. In all these cases we see marked depression coincident with abundant oxygen after a period of oxygen deficiency.

Probably in all cases, excessive blowing off of carbon dioxid occurs during the period of oxygen deficiency and excessive breathing. The deficiency of oxygen, meanwhile, either by itself or through some incomplete combustion product, keeps respiration working, and working even excessively. But when a full supply of oxygen is renewed, this anexemic stimulus is removed. The deficiency of carbon dioxid then allows respiration to fail. The condition of deficiency of carbon dioxid is called "acapnia," a word derived from the Greek, literally meaning smokelessness. It tends to be overcome spontaneously as the carbon dioxid produced in the body reaccumulates in the blood. But this may require a long period, and while the condition lasts, it profundly disturbs the acid-alkali balance in the blood. It forces alkali out of the blood and may induce an extreme and rapid decrease in the alkali reserve. It thus induces what is now called acidosis.

It used to be common to think that deficiency of oxygen was necessarily associated with excess of carbon dioxid in the blood. This may perhaps be the case in drowning, but under nearly all clinical conditions we actually find anoxemia and acapnia associated. This combination of deficiency both of oxygen and of carbon dioxid is capable of inducing profound functional disturbances. Not only is the blood alkali lowered, but such conditions as edema of the brain and congestion of the lungs may result.

The field in which inhalation of oxygen plus carbon dioxid has made its most definite and extensive success is that of carbon monoxid asphyxia. In nearly all our

cities the number of deaths from this cause is large. As a cause of mortality, it is nearly as important as diabetes. Carbon monoxid has probably displaced lead as the most important industrial poison. More than 400 deaths a year are assigned in New York City to the city gas. Every stove, in a dwelling house, that can be checked to the point of incomplete combustion may give off carbon monoxid and asphyxiate its owner and his family. It is the chief toxic constituent of automobile exhaust gas. Even a Ford produces at least a cubic foot of carbon monoxid a minute, enough to render a small closed garage deadly in five minutes. Men who work in garages and repair shops are almost daily subjected to partial intoxication by carbon monoxid. If a man is overcome by inhaling a fairly high concentration of carbon monoxid under any of the foregoing conditions, his legs give way under him before he realizes his own condition. If he is fortunate enough to be discovered before death, he is dragged or carried out of the garage, out of the trench in the street, or away from the blast furnace, where he has been working. If he has stopped breathing, his rescuer immediately applies the prone pressure method. After such a short but acute gassing, a man who survives without having been treated with oxygen and carbon monoxid is always acutely sick with splitting headache and nausea, lasting for two or three days. This is due to a congestion and edema of the brain. Those who are treated with carbon dioxid and oxygen, often escape the after effect entirely. Heretofore, about one-third of all persons severely gassed, but not dying under asphyxia, have later died in the hospital from pneumonia. After severe but not fatal gassing extensive râles are found to be common. In view of these facts, it is highly significant that not a single patient in all those of whom the author has record, has developed pneumonia after being treated by the inhalation method. The pulmonary

congestion, like the brain edema, seems to be cleared up by this treatment.

The most rapid and most effective method of eliminating a volatile poison from the body is to administer an inhalation of oxygen or air containing enough carbon dioxid to increase the volume of breathing four or five times. Men overcome by fumes of gasolin and other volatile substances have thus been successfully treated.

But the most interesting cases are those of acute alcoholic intoxication. Ethyl alcohol is burned in the body, but methyl alcohol is not. It may be accumulated from day to day until disastrous symptoms, particularly blindness, develop. Observations by H. W. Haggard, indicate that the lungs are probably ordinarily almost the sole avenue of elimination of this poison and that stimulation of breathing by inhalation of carbon dioxid is, therefore, an almost specific treatment for this important form of poisoning.

Morphin poisoning is due to failure of respiration. The respiratory center becomes relatively insensitive to the stimulus of carbon dioxid. In other words, more carbon dioxid is necessary in order to induce breathing. When morphin is administered prior to anesthesia, it sometimes happens that the patient is unusually sensitive to the drug and that respiration is dangerously depressed. In such cases, inhalation of carbon dioxid in oxygen or air has proved strikingly effective, when otherwise the patient almost certainly would have died.

The use of inhalations containing carbon dioxid to stimulate respiration and accelerate the elimination of volatile anesthetics is now on a firm basis of proved clinical value. It has saved a number of lives in several hospitals. It has been found useful as an adjunct to ethylene anesthesia. After anesthesia, respiration is often so much depressed that the elimination of the anesthetic is very slow, especially when considerable amounts of ether have been used, and the patient under-

goes a prolonged period of partial asphyxia. The inhalation of carbon dioxid in air or oxygen induces an increase in the volume of breathing, which rapidly ventilates the anesthetic out of the body. It thus prevents the occurrence of the usual period of partial asphyxia. In practice, it is found that vomiting, nausea and gas pains are greatly decreased. Arterial pressure is quickly restored to a normal level and the blood alkali is brought back to normal.

In acute cases of pneumonia, oxygen inhalations may shift the balance between a fatal outcome and recovery. It is obvious that, under the conditions of respiratory distress existing in pneumonia, carbon dioxid should not be added. The H. H. inhaler could be effectively adapted to administering oxypen in pneumonia.

F. T. Hunter and S. G. Mudd[9] administered carbon dioxid in cases brought into the hospital on account of acute alcohol intoxication, using an apparatus identical with that described by Henderson and Haggard and used by White for de-etherization, consisting of a tank of carbon dioxid, a reducng valve, a water bottle to regulate the flow of gas, and an open slot mask. The latter is so constructed that the room air on being inspired is increased in carbon dioxid content by a steady stream of the gas, and the expired air containing alcohol vapor is blown out into the room through a slot in the mask. The effect of this is to increase the pulmonary ventilation with a rapid lowering of the tension of alcohol in the alveoli. Lung ventilation was increased from four to eight times the normal. The effect being due more to an increase in the volume for each breath than to an increased rate. They secured by this means rapid revival from coma. Lesser degrees of intoxication did not show such striking improvement. An experiment was performed which apparently showed that the alcohol in the blood may be lowered more rapidly by the increased lung ventilation from carbon dioxid adminis-

(9) Boston Med. and Surg. Jour., June 5, 1924.

tration than would be the case without it. The authors believe that in cases of methyl alcohol poisoning carbon dioxid would be even more efficacious, as, due to its lower boiling point, it has a higher partial pressure than ethyl alcohol.

Oxygen

Therapeutic Use of Oxygen. G. Bourne[1] deplores the fact that oxygen is at present used only as a measure of emergency and even of despair. When all else has failed, the baleful hiss of the gas is heard in the sick room. Indeed, it is often ordered for its effect upon the patient's friends and relatives. Decease is deemed incomplete or, indeed, hardly respectable without the presence of an oxygen cylinder at the terminal scene. This lack of enthusiasm for it as a drug is entirely due to the fact that hardly any is absorbed when given by the funnel method, and therefore no definite beneficial results can be put down to its use.

Anoxemia is the only indication for oxygen therapy. Anoxemia is the name given to the condition in which symptoms occur as a result of lack of oxygen. This lack of oxygen leads to fatigue of the respiratory center and shallow breathing, which causes diminished aeration of the blood. Such a vicious circle can be prevented, and should never be allowed to occur.

Cyanosis is probably the best rough clinical guide to the presence of anoxemia, but does not necessarily indicate its degree. In severe anemias, cyanosis cannot occur, however great the oxygen-lack may be. In this condition, however, there is no impediment to full saturation of what corpuscles there may be left, and a raised oxygen-tension in the inspired air can add little to the 95 per cent. saturation they already hold. In pneumonia the rate of blood-flow appears to be normal or even increased. Thus cyanosis in that disease, apart from heart-

(1) Practitioner, January, 1924.

failure, will be directly proportional to the degree of arterial anoxemia.

In heart-failure, on the other hand, the cyanosis will be largely due to the partial stagnation of blood in the tissues, which permits these to deprive the hemoglobin of much of its oxygen.

Raising the oxygen-tension in the inspired air will logically meet either contingency; but it is evident that the cyanosis and anoxemia of pneumonia will theoretically be removed completely, whereas in heart failure the drug is mechanically baulked of its complete success, for although complete oxygenation may be induced, the stagnation still persists. In the latter case, however, a raised intake of oxygen must result in a cure of the arterial anoxemia if present, and therefore in some reduction of the stagnation anoxaemia also. Moreover, there is some evidence that oxygen has a direct stimulating effect on the heart-muscle itself.

The type of pneumonia best influenced by oxygen is that in which, in addition to consolidation, considerable edema is present adjacent to this. Presumably, whereas the swollen alveolar walls are relatively impenetrable to a normal oxygen-tension, they yield to one that is somewhat raised. Clinically therefore, the pneumonia most likely to be benefited by oxygen is the one accompanied by some cyanosis and many râles and rhonchi. Oxygen should, however, be given as a routine in all cases of pneumonia.

Success depends entirely upon the proper methods of giving oxygen. The funnel method generally in vogue is very nearly useless, expensive and unpleasant. The oxygen chamber is ideal, most especially in carbon-monoxid poisoning which is best treated by forcing oxygen into solution in the plasma, for the corpuscles only reluctantly give up the former gas. Unfortunately it is not generally available.

The Haldane mask is unsuited to a patient who is seriously ill. The suggestion of a feeling of suffocation,

the cumbersomeness of the whole apparatus, the weight and the serpentine coils of the heavy tubing make it annoying to a patient whose mental balance is naturally over-sensitive.

The method of choice in general practice is the intra-nasal method, passing the gas to the posterior nares through a rubber catheter the sides of which have been lubricated with a procain ointment. The catheter may be strapped to the cheek, but the writer has found that a light portable apparatus is more useful. Briefly, a circlet round the head holds a small flat plate of aluminium on the forehead. Screwed to this is an aluminum wire with a loop at either end holding the rubber catheter. The lower loop holds it at the entrance to the nostril, thus preventing any slip. (cf. Pract. Med. Series, 1922, vol. VI, p. 80, Fig. 4.) There is a considerable economy in oxygen consumption.

If anoxemia is suspected, or if cyanosis is present and is taken as a rough clinical guide to anoxemia, oxygen should be given till this disappears. Having banished the cyanosis, it will probably be found that a few administrations, lasting one hour each per day will be sufficient. In cases of severe oxygen-lack there is no reason why oxygen should not be given continuously day and night. The intra-nasal apparatus, if properly adjusted, does not interfere with sleep.

Even more important is the treatment of the patient's mental condition. Thanks to the number of death-bed scenes at which the drug has been a gloomy and an impotent witness, oxygen is regarded with horror by many patients. When the medical attendant suggests its use, he is regarded with as much alarm as though he were already foretelling the end. It must be carefully explained to the patient that nowadays oxygen is given as a drug regularly and to treat definite conditions; that the old-fashioned idea of using it merely as an emergency measure has been discredited; and that active cooperation on the part of the patient to over-

come any temporary slight inconvenience is necessary. A final point must also be explained. The patient must be told that in spite of the oxygen he will perhaps still remain dyspneic, for the dyspnea of pneumonia is often toxic rather than anoxemic in origin; that in spite of the persistence of the breathlessness, the drug is really doing him good and is warding off further troubles.

TRANSFUSION

Citrated Blood Transfusion. An experimental study of the toxicity of sodium citrate in exsanguinated dogs leads Minas Joannides and Angus L. Cameron[2] to conclude that two-tenths per cent. citrated blood is highly satisfactory as a transfusion medium in exsanguinated dogs, provided the amount of sodium citrate injected does not exceed 1 gm. which is the maximum safe dose for animals weighing between 9 and 18 kilograms. There is a prompt and permanent rise in blood pressure and a permanent improvement in the general condition of the animals. Exsanguination does not increase the susceptibility of a dog to the toxic effects of sodium citrate.

In comparing this experimental work on dogs with actual clinical cases, it should be emphasized that the commonly accepted maximum safe dose of sodium citrate for the human being is 5 gm. Therefore, if analogous conditions prevail in man as compared to the dog relative to the toxicity of sodium citrate, *one may safely transfuse an exsanguinated human being with as much citrated blood as is ever used* in a transfusion and still be far under the danger point so far as the amount of sodium citrate administered is concerned, for 2,500 c.c. of 0.2 per cent. citrated blood would contain only 5 gm.

As a result of an experimental study upon lower animals, George R. Love[3] also arrives at the conclusion

(2) Jour. Amer. Med. Ass'n., Apr. 12, 1924.
(3) Jour. of Lab. and Clin. Med., December, 1923.

that sodium citrate, in the dose used and at the rate injected in blood transfusions, produces no effect upon circulation which would militate against its use as an anticoagulant. By doses of 30 mgm. for each kilogram or more the heart muscle of dogs is depressed, the vasomoter center is stimulated, as are the cardio-inhibitor and cardio-accelerator centers and the endings of the accelerator nerves to the heart. There is some evidence that large doses cause active dilatation of the vessels of the kidney. Plethysmograph tracings of the extremities and intestines show no peripheral action upon blood vessels.

L. Colebrook and E. J. Storer[4], on the other hand show experimentally that *decalcifying agents reduce the bactericidal power of blood.* They ascribe this result to interference with some of the functions of the leukocytes. Hence citrated blood should not be employed for "immunotransfusion."

Intraperitoneal Injection of Blood. H. O. Ruh and J. E. McClelland[5] have demonstrated by experiments on guinea-pigs and dogs that blood of the same species is very rapidly absorbed from the peritoneal cavity and that absorption takes place largely through the thoracic duct.

In order to determine, if possible, the difference in absorption of defibrinated, citrated or whole blood, three series of guinea-pigs were injected intraperitoneally with the three different bloods. They find that the injection of whole blood, which is the most simple, gives no more reaction than modified blood and is, therefore, to be preferred. They have obtained encouraging results in the few cases in which the authors had the opportunity to use it, and believe that this form of transfussion could be made a valuable clinical procedure in selected cases of sick infants, not only in cases of hemorrhagic disease of the new-born and in anemia, but also in many other conditions.

(4) British Jour. Exper. Path., April, 1924.
(5) Ohio State Med. Jour., November, 1923.

Hans Opitz[6] recommends in severe anemia of infants, in cases where intravenous injection is difficult or impossible, the intraperitoneal injection of defibrinated blood, which in two cases reported produced very satisfactory results. Experiments upon dogs and rabbits showed absorption and absence of adhesions after the use of citrated as well as defibrinated blood. Typing to avoid agglutination or hemolysis are as necessary here as in intravenous infusion.

Serum the Best Preservative for Blood and Other Cells. H. Dold[7] finds that of all the solutions examined —physiologic salt solution, Ringer solution, Tyrode solution, normosal, albumen-free serum filtrate, serum, citrate plasma—the serum was best suitable for the preservation and keeping alive of leukocytes, erythrocytes, blood platelets and other body cells. In serum, providing sterility and uniformly low temperature of about +5° C., is secured, leukocytes may be kept for weeks, blood platelets for several days.

Acacia Saline as Heart Stimulant. Carl Junkmann[8] studying the effect of acacia saline upon the isolated frog's heart, arrives at the conclusion that acacia has the power of improving the action of the heart especially when its musculature is exhausted and that this action is independent of its calcium content or its viscosity. Acacia is actually superior to digitalis in improving the action of the fatigued heart and in this respect is similar to caffein but more prolonged in its action. As it is incapable, however, of antagonizing the damage produced by chloral, a combination of caffein and acacia might be of advantage in the treatment of heart weakness.

Gum-Glucose Solution in Postoperative Shock. R. C. Coburn[9] finds gum-glucose solution a good measure for combating shock and hemorrhage. Though blood

(6) Klin. Wochenschr., Apr. 29, 1924.
(7) Ibid., Apr. 8, 1924.
(8) Ibid., Aug. 26, 1924.
(9) Jour. Amer. Med. Ass'n., May 31, 1924.

transfusion stands at the head of the list of the means used for both the prophylactic and the restorative treatment of surgical shock and hemorrhage, in many cases when serious depression occurs during or soon after the operation, blood transfusion usually is not available soon enough. To tide the patient over till he can be typed and a donor arranged, 250 c.c. of a 6 per cent. solution of gum acacia and 20 per cent. glucose introduced intravenously at the rate of 4 c.c. a minute should be used. It increases blood pressure immediately, the patient becomes decidedly more pink, and there is every indication of a pronounced general improvement. The improvement may be so decided that in some cases blood transfusion may not be necessary, even though it seemed imperative at the time the gum-glucose was administered. Such patients, however, must be carefully watched, for if there is not a genuine systemic reaction the blood pressure will fall again after a few hours, and the patient will again be in a critical condition.

OSMOTHERAPY

Cerebro-Spinal Osmotherapy

Magnesium Sulphate Superior to Sodium Chlorid for Relief of Intracranial Tension. Temple Fay[1] demonstrated by experiments on dogs and clinical observation that magnesium sulphate, in the same isotonic solution (25 per cent.), was almost twice as efficient as the sodium chlorid (3 per cent.) under identical circumstances. The use of sodium chlorid by bowel was found to be attended with great discomfort, such as thirst, and often nausea, and the effects were transitory and not so complete as those obtained from the use of magnesium sulphate. The explanation lies in the fact that sodium chlorid is dialyzable when in the intestinal tract, and

(1) Jour. Amer. Med. Ass'n., Mar. 8, 1924.

that its influence is first exerted on the vascular bed about the intestinal walls with extraction of fluid from the circulation. The 3 per cent. sodium chlorid, at the same time, being hypertonic to the chlorid content of the blood, is rapidly absorbed and enters the blood system, which in turn becomes hypertonic, owing to this increase in sodium chlorid. It in turn extracts fluids from tissue spaces, and especially the ventricular system. In the meantime the sodium chlorid in the blood stream has entered tissue spaces, including the ventricular system. It will be apparent that, as soon as the blood sodium chlorid content falls, owing to kidney elimination, below that of the tissue sodium chlorid, the reverse processes will become manifest, and fluids from the blood stream then add water to the tissue bound sodium chlorid and cause a secondary wave of tissue edema with an increase in intracranial pressure. This secondary wave of pressure has been noted clinically, and though transitory, its effect should be actively combated if the patient shows signs of medullary compression.

Magnesium sulphate, on the other hand, is nondialyzable and, not being absorbed into the blood stream, exerts its entire effects on the vascular bed about the intestinal wall; hence the direct extraction of fluid from the circulation and the secondary withdrawal of ventricular or tissue bound fluids brings about dehydration, for the circulation calls on all the available body fluids to compensate for the depletion in blood volume by way of the intestinal tract.

Great care must be taken in the treatment of acute traumatic cases to distinguish between cases which show symptoms of intracranial pressure and those with increased tension, plus profound shock. In the treatment for concussion and intracranial tension, dehydration is necessary to relieve the cerebral congestion, and magnesium sulphate may be used to deplete blood volume and combat increased fluid tension of the brain. If, however, following head injuries, as is so frequently the

case, the patient has lost large quantities of blood, or sustained injuries which have produced a profound state of shock, then hydration is contraindicated; in fact, using an agent to deplete an already impoverished and failing circulatory system is but to hasten the final termination of the case.

Cases of increased intracranial tension show a gradual fall in respiratory rate and rising temperature readings. In the early stages, the pulse rate too will fall rapidly with the respiratory rate. Later, the pulse may rapidly rise to 160 and over, in the final stages of severe concussion. It is, therefore, necessary to regard carefully the respiratory rate as an index of intracranial tension. The fall may be gradual to zero, or Cheyne-Stokes respiration may supervene. (Fig. 6). If the case

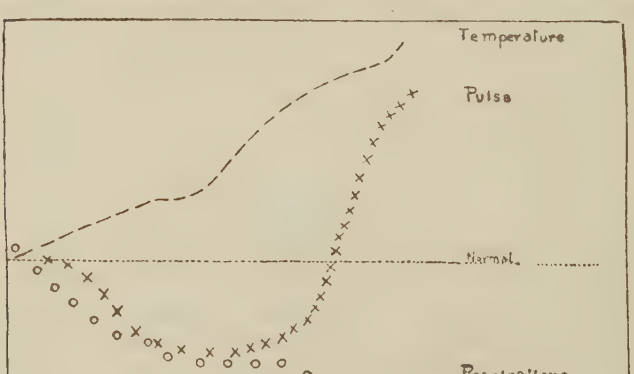


Fig. 6.—Stages in acute cases of intracranial tension; the first stage appears early and therefore may be missed before the patient comes under observation; in the second stage, the depressant effect from vagus irritation may have ceased and the pulse rises rapidly with the temperature; respiration always below normal.

is seen sometime following the injury, the pulse may have passed over its original depressed rate to a second phase with rapid pulse which simulates so closely that

seen in shock. In this stage, however, two things will help to differentiate the conditions from that of true shock; the respirations will be found to be below normal and the temperature rapidly ascending with the pulse. (Fig. 6). As is well known, in shock the reverse is to be found, and the respiration is that of air hunger and above the normal rate; the temperature is well below the normal line and the pulse is rapidly rising. (Fig. 7.)

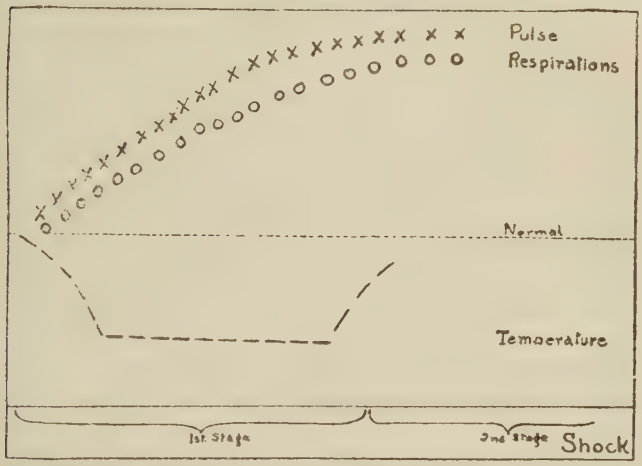


Fig. 7.—The usual picture of profound shock (surgical): the temperature, at first subnormal, may later rise high above the normal line; respirations above the normal.

Cases of increased intracranial tension, plus profound shock, present the dilemma, as to which phase to treat actively. This usually solves itself in that the shocked condition of the patient prohibits progressive tissue edema of the brain and the case must be carefully watched so that fluid may be added or withdrawn, as the symptoms of one or the other become more serious.

The author uses in his practice 45 gm. of crystals of magnesium sulphate, by mouth every fourth hour, if necessary, to produce the desired result; or, if the patient's condition makes it impossible to give the drug by mouth because of vomiting, stupor or delirium, then the admin-

istration by rectum of 90 gm. of crystals in 178 c.c. of water, repeated every fourth hour, has been found as effective but not as rapid a means of counteracting the rising intracranial tension. The beneficial use of this salt in cranial injuries has been well established in the author's clinic.

He also reports two cases of overdehydration in which it was noted that the respiratory rate rose far above the normal, and the picture of air hunger and rapid pulse gave the appearance similar to that seen in severe hemorrhage with loss of blood volume. When fluid was forced on the patient the pulse, temperature and respirations again returned to normal. It must therefore be borne in mind that overdehydration is possible by the active use of hypertonic salt solutions. The respiratory rate would seem to be the most reliable index of intracranial pressure disturbances throughout.

Since the inauguration of this method for treatment of acute cases of cerebral trauma, it has become unnecessary to subject patients to the added operative risk of decompression and the subsequent disfigurement, so that in the last two years decompression for concussion of fractured skull has almost been abandoned by this clinic, excepting only in those cases in which the middle meningeal hemorrhage syndrome or definite signs of localization could be demonstrated.

Raising Cerebrospinal Fluid Pressure Relieves Lumbar Puncture Headache. H. C. Solomon[2] carried out observations on human subjects who were having lumbar puncture for diagnosis or treatment, and who willingly coöperated in the experiments. He found that in the majority of cases an intra-muscular injection of 1 c.c. of obstetrical pituitary extract causes a rise in the cerebrospinal fluid tension of from 10 to 100 per cent. (av. 35 per cent.) measured by a manometer connected with the lumbar subarachnoid space. This rise begins nearly always in from three and one-half to five minutes

(2) Jour. Amer. Med. Ass'n., May 10, 1924.

after the injection of the drug, and continues for a period of at least 45 minutes, which is the length of time that the manometric readings were made. (Fig. 8.)

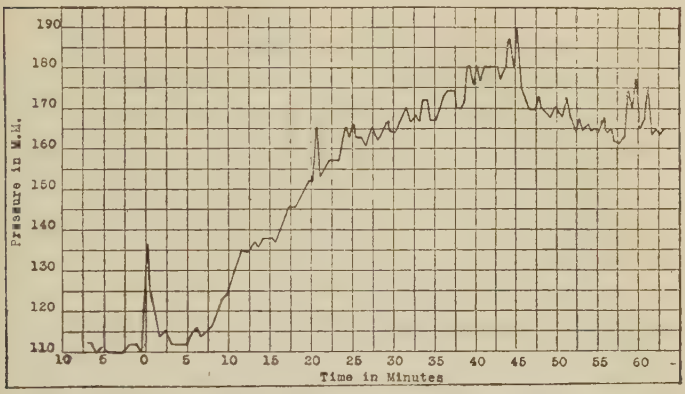


Fig. 8.—Effect of intramuscular injection of pituitary extract on cerebrospinal fluid pressure.

Whether this effect is due to an increase in the amount of cerebrospinal fluid, or whether it is due to the effect on the circulation, is not shown by these experiments.

Pituitary extract, injected intraspinally, that is, injected directly into the cerebrospinal fluid, has no effect on the cerebrospinal fluid pressure.

Epinephrin injected intramuscularly caused very little change in the cerebrospinal fluid pressure level in the majority of cases. When epinephrin is given intravenously, it causes a very marked increase in blood pressure, and in these circumstances, an increase in the cerebrospinal fluid pressure. Given into the subarachnoid space, it causes no variation in the fluid pressure.

The intravenous injection of from 100 to 200 c.c. of distilled water, a hypotonic solution, causes a definite rise in the cerebrospinal fluid tension, much the same as that produced by 1 c.c. of pituitary extract, which lasts for a considerable period of time, and in some observa-

tions considerably over an hour. In other cases it was found that after thirty minutes, the fluid pressure began to fall and at the end of an hour had reached its original level. (Fig. 9.)

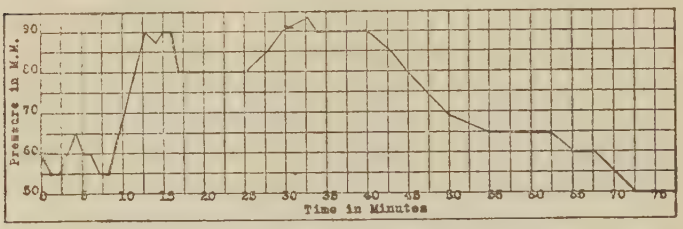


Fig. 9.—Effect on spinal fluid pressure of intravenous injection of 200 c.c. distilled water.

It seemed worth while to investigate the effect of such pressure raising injections on lumbar puncture headaches, as patients who develop lumbar puncture headaches have a cerebrospinal fluid pressure during their headaches which is considerably less than that obtained when the original puncture was made.

The author reports five cases, in which relief was obtained by the use of either of these methods or a combination of the two. In some cases the effect of pituitary extract was very striking; and to the patient, wonderful. In a few cases in which the effect was marked and immediate, it lasted from five to ten hours and then wore off, the headache returning. In several of these cases a second injection or even a third had an effect similar to the first; that is, the headache was relieved.

Peritoneal Osmotherapy

Osmotherapy in Peritonitis. Joseph K. Narat[3] experimented with peritoneal "osmotherapy" by studying systematically the efficiency of intra-abdominal injections of hypertonic sugar solution in peritonitis of rabbits. He found that a normal rabbit can stand safely

(3) Ann. Surg., September, 1923.

an injection of one-fiftieth of its weight in 20 per cent. dextrose. After injection of a larger amount of dextrose, some of the animals died with cramps because of a rapid dehydration of the blood.

In order to determine the rate of secretion he injected the same amount of dextrose into a group of animals and killed them at certain intervals to test accurately the quantity of liquid secreted. The experiments showed that following injection of 50 c.c. of 20 per cent. dextrose there were in the peritoneal cavity: after 1 hour, 85 c.c. colorless, clear, partially coagulated liquid; after 2 hours, 70 c.c.; after 3 hours, 110 c.c.; after 3 hours 20 minutes, 140 c.c.; after 4 hours 30 minutes, 120 c.c.; after 5 hours 30 minutes, 90 c.c.; after 24 hours, 0. By injecting physiologic salt solution hypodermically he was able to increase still further this enormous transudation. For example, in one rabbit he obtained 150 c.c. of liquid two hours after dextrose injection, and in another one as much as 200 c.c. seven hours later; this shows an increase of four times the amount injected.

In the second group of animals he produced peritonitis by injecting a culture of staphylococci the virulence of which was intensified to such a degree as to cause death in approximately 48 hours. The dextrose was injected 4 to 24 hours after the introduction of staphylococci. The injections were repeated three to six times, at intervals of six to twelve hours. The results were as follows: all the twenty control animals, which received injections of staphylococci only, died within 24 to 48 hours. Of the animals which after production of peritonitis received glucose injections, only one died after 36 hours. Three died after six, nine or eleven days, respectively. The remaining fourteen survived the experiment, but with exception of one, were killed to determine the pathologic changes about three weeks later. In all these animals he found a pronounced free peritonitis chiefly of purulent-fibrinous character; in two cases there were caseous changes. In all the animals it was a free, disseminated

peritonitis. The mesenteric blood-vessels and lymph-nodes were enlarged, there were many adhesions between the intestines, and a large amount of pus was found in the abdominal cavity. These experiments prove conclusively, that it is possible to save the rabbits with peritonitis by intra-abdominal injections of hypertonic dextrose solution and to succeed even if the injections are first given 24 hours after the introduction of staphylococci.

To meet the objection that the sugar has merely a nutritional value and the good results are not due to the osmotic action, the author injected in two rabbits the same amount of dextrose solution hypodermically. Both animals died within 24 hours. Thus a hypodermic injection of sugar was without therapeutic effect. Many blood smears were prepared; neither red nor white blood corpuscles showed any changes after dextrose injections.

He ascribes the favorable results to the fact that the bacteria and their toxins are distributed through a greater amount of liquid when glucose is injected and they enter the blood stream more slowly, thus giving the organism more opportunity to counteract them.

The advantages of sugar solution over any other hypertonic solution are listed by Narat as follows:

1. Sugar prevents coagulation of the blood; thus the resorption of the liquid blood which may be found in the peritoneal cavity is made possible and the bacteria are deprived of an excellent culture medium in form of blood-clots. The sugar may also act as a prophylactic by preventing the formation of postoperative thrombosis.

2. Sugar counteracts the acidosis which develops following starvation and dehydration of the body by sparing the combustion of fat and proteins with the resulting formation of toxic acid bodies.

3. Sugar possesses the power to divert the bacteria from the production of proteolytic enzymes and toxins to the formation of acid products, which are generally

harmless while the alkaline are injurious and dangerous. Many germs cause fermentation of carbohydrates and production of lactic acid and when the supply of the carbohydrates is exhausted they decompose the peptones and form toxins, ptomaines and other injurious substances.

4. Sugar has a certain bactericidal power. When sugar is added to a culture of streptococci, the number of colonies is less than in a similar culture without sugar and the hemolytic zone smaller.

5. Sugar is a food easily assimilated and with a high nutritive value as well as a stimulant to the mechanism of cell metabolism. The sugar content of the blood increases as much as three times after intraperitoneal injection of glucose; but practically no sugar is eliminated by the kidneys.

6. Due to its heavy, syrup-like consistency the glucose solution is a good mechanic isolator for the intestines, and in this way removes the greatest obstacle to permanent drainage, *i.e.*, the formation of adhesions and matting together of the coils of intestines.

Since this method is absolutely harmless and gives encouraging results the author feels justified to suggest that this treatment be used in human beings in suitable cases. About 500 c.c. of 20 per cent. dextrose solution would be the proper amount to begin with, the injections could be repeated through the drainage tube every six to twelve hours. In addition, of course, the fundamental principles for the treatment of peritoneal inflammation have to be strictly observed, namely, gastric lavages, Fowler's posture, permitting absolutely nothing to be put into the stomach, rectal feeding, introduction of liquids into the system by proctoclysis, hypodermoclysis or intravenous infusion, and avoidance of purgation.

Intestinal Osmotherapy

Sodium Chlorid in Treatment of Intestinal Obstruction. R. L. Haden and T. G. Orr[4] point out that a fall in the chlorids is as fundamental a change taking place in the blood after the upper intestinal tract is obstructed as is the increase in nonprotein nitrogen. At the same time there is a diminished excretion of chlorids in the urine. With vomiting there is some loss of chlorids; but that vomiting does not explain the condition is shown by the following facts. This loss also takes place in rabbits with the intestine obstructed, and rabbits cannot vomit. A similar change in chlorids occurred also in one patient who did not vomit at any time, and has been repeatedly observed in dogs in the absence of any significant loss of chlorids by vomiting. The loss of chlorids by vomiting only accentuates the intoxication.

Dogs with obstruction of the duodenum have been treated with sodium chlorid both from the beginning of the obstruction and after the development of the toxic symptoms. Such dogs have been kept alive 27 and 28 days by the daily subcutaneous administration of physiologic sodium chlorid solution when treated from the beginning of the obstruction. Control dogs of the same weight treated with the same quantity of sterile distilled water died in three or four days. After the characteristic rise in the urea and nonprotein nitrogen and fall in the chlorids of the blood has taken place, the administration of sufficient sodium chlorid will usually cause a return of these changes to normal and a prolongation of the life of the animal.

It is quite evident that the sodium chlorid acts in some protective capacity. Haden and Orr report a number of cases that serve to emphasize the importance of the administration of chlorids in the treatment of intestinal obstruction toxemia. They suggest that in cases of acute intestinal obstruction 1 gm. of sodium chlorid for each

(4) Jour. Amer. Med. Ass'n., May 10, 1924.

kilogram of body weight be given as the initial dose, and continued daily in sufficient quantity to return and maintain the sodium chlorid in the blood within normal limits.

Claude F. Dixon[5] also reports five cases of duodenal intoxication in which the effect of treatment with chlorid was remarkable, both in clinical and in chemical changes. The administration of sodium chlorid causes a decrease in the carbon dioxid combining power and an increase in the plasma chlorid content. Following the administration of a sufficient amount of sodium chlorid, the urine often becomes completely normal in from twelve to 36 hours.

Dixon also points out that patients suffering from intestinal occlusion, resulting in duodenal toxemia, are in much better condition to undergo operation if preliminary treatment with chlorid is instituted. Postoperative vomiting, which often follows gastro-enterostomy, is diminished or abated by the administration of sodium chlorid. Patients with functional stasis and vomiting, if there is no obstruction, likewise improve remarkably or recover following this treatment.

Brown, Eusterman, Hartman and Rowntree have used calcium chlorid and dilute hydrochloric acid and large amounts of fluids in the form of physiologic sodium chlorid solution intravenously, subcutaneously, and by rectum; and Ringer's solution, also, in the treatment of duodenal intoxication. Hydrochloric acid probably serves the same purpose as sodium chlorid in this condition, but must be given in a very dilute form. In instances in which there is complete intestinal occlusion, its administration is not easy. Calcium chlorid also seems quite efficient, but large amounts of chlorid are often needed. Calcium cannot be administered subcutaneously because of the extensive necrosis that results. Caution must be used in its intravenous administration for the same reason. Sodium chlorid may be given in

(5) Jour. Amer. Med. Ass'n., May 10, 1924.

large quantities, subcutaneously, intravenously, by a duodenal tube, or by proctoclysis. It may also be administered in the form of tablets covered with phenyl salicylate in cases of duodenal toxemia in which the obstruction is below the pylorus, and in functional cases in which there is stasis without obstruction. There is therefore little or no doubt that sodium chlorid seems to be the chlorid of choice in the treatment of duodenal intoxication.

DIETOTHERAPY

Fluids

Best Time for Giving Fluids. P. L. Violle[6] finds, as the result of his researches, that the time for giving fluid varies in different affections. Thus, in cardiovascular affections, beverages should be taken with patient reclining, and preferably on awaking in the morning and on retiring for the night, on account of the better clinostatic than orthostatic elimination. At other times, drinks should be taken in small quantities and not during meals.

When gastric dilatation exists, beverages should be taken only a long time after meals, and in small, divided doses, the patient being recumbent.

In the presence of profuse diarrhea, beverages need not be reduced, but should be so prescribed in sufficient quantity as to bring the total twenty-four hour quantity of urine as nearly to the normal as possible.

In portal hypertension the quantity of liquids which produces most abundant elimination of urine should be determined by making a number of trials. Beverages should not be taken with meals in order not to add physiologic hypertension to the portal hypertension already present.

(6) Lancet, May 17, 1924.

In edema due to chlorid retention, the patient should not receive chlorids with the food, and the beverages should be adjusted to the reduced elimination commonly present in cases of this kind.

Dextrose

Prescribe Dextrose Rather Than Glucose for Intravenous Injection. W. R. Cathcart[7] calls attention to the fact that the term "glucose" was originally used only in a chemical sense as synonymous with dextrose. Outside of strictly chemical circles, glucose is understood to mean the dextrose of glucose containing syrup made from corn starch or potato starch, analyses of which show a dextrin, (about 30 per cent.) sucrose, and mineral ash content in addition to a dextrose value of about 30 per cent. The presence of dextrin, sucrose, and mineral salt may be undesirable from the standpoint of injectional application. On the other hand, the mineral salts and dextrin may be distinctly beneficial for other purposes. It has been suggested that dextrin is even a desirable constituent of the product for injection, because it is changed into dextrose gradually, and the absorption of dextrose is therefore not so likely to be more rapid than the system can utilize advantageously.

The value of dextrose for the various forms of injection is perfectly well known. In the present state of knowledge it is clearly advisable to specify "chemically pure dextrose" for this purpose rather than simply "glucose". Inquiry discloses that *the druggist will most assuredly supply glucose syrup (corn syrup) whenever simply glucose is called for.* During the last few years manufacturing processes have been so improved that dextrose or glucose in the chemical sense

(7) Therap. Gaz., Aug. 15, 1924.

(a product heretofore rarely found outside of the chemical laboratory) has now become a regular fixed article of commerce.[8]

HIGH CARBOHYDRATE DIET

Therapeutic Uses of High Carbohydrate Diets. T. Izod Bennett[9] believes that the value of high carbohydrate diets is not sufficiently appreciated. Carbohydrates are usually completely absorbed. Even in diseases where diarrhea is present it is unusual for any carbohydrate to escape complete digestion. Very different is the state of affairs as regards the fats and the proteins. In diarrheal diseases, in jaundice, or with faulty pancreatic secretion, the loss of one or both of these constituents may be very considerable.

After absorption the carbohydrates require no great work on the part of the tissues in the process of their combustion and the elimination of their end-products. Proteins, on the other hand, after their absorption as amino-acids, must for the most part be substantially changed by the liver. The denitrification of these bodies calls for an appreciable amount of work by that organ, and the end-products so formed—urea, uric acid, and other nitrogenous substances—charge the blood with, at best, inert products, which require work from the kidneys before they can be eliminated. Nor are the fats less exacting. We know that they are, after absorption, less readily burnt up than the other foods. An actual provision of oxygen is called for for this purpose, and when this is deficient, aceto-acetic and hydroxybutyric acids—poisonous substances—may be produced with very definite ill-results.

(8) For Dextrose-Insulin administration see "Insulin." For osmotherapeutic use of dextrose see under "Osmotherapy."
(9) Lancet, July 5, 1924.

Hyperglycemia does not occur in any but a diabetic person, unless very great amounts of glucose itself be given by the mouth. The digestion of starch is slow enough to secure a steady and prolonged absorption of glucose without great excess at any given moment.

One most important effect of such a diet is its action upon the flora of the alimentary canal. Two great groups of organisms are normally present, whose characters are widely divergent. These are (1) the indol-producing group, which live upon the products of protein digestion, and (2) the acidophilus group, which prefer a carbohydrate diet. The first of these groups is thought to play a part, if indeed its members be not the direct cause, in many generalised infections, they are typical putrefactive organisms, and when present in abundance, ethereal sulphates and indican are found in the urine. This group becomes rapidly replaced by the acidophilus group of organisms as soon as the patient is put on a high carbohydrate diet. One caution must be voiced here; the acidophilus group form gas with many sugars and this excess of carbon dioxid does, in some cases, cause a certain amount of intestinal distension. It is not noticeable in the majority of cases, and when it does prove a difficulty it can often be overcome by giving saccharose or certain other sugars instead of glucose.

The author lists the following conditions in which high carbohydrate diets are useful.

If a wasting baby has hard constipated motions consisting largely of fat and calcium soaps, great benefit can usually be secured by reducing the fat in the patient's diet and increasing the carbohydrate by means of dextrimaltose or some similar preparation.

Pneumococcal pneumonia provides an excellent illustration of the utility of such diets in acute diseases. The disease is too violent in its onslaught for normal digestion to be possible. As the period before the crisis rarely lasts ten days, it becomes clear that a highly

digestible dietary, containing readily assimilable energy, is all that can be needed during this time. Glucose is the ideal substance for such a purpose, and repeated feeds of strong glucose solution is of great service. Beyond this, all food given before the crisis need be no more than a placebo, and it is, indeed, of benefit to keep its amount very small.

In *typhoid and paratyphoid infections* the utility of carbohydrates has long been recognised, but gas formation must be watched for, as it may sometimes prove very uncomfortable.

In *Bacillus coli communis infections* a high carbohydrate diet with very reduced protein, often appears to be of the utmost service in checking an attack and preventing relapses. In view of their chronic nature, the diet must be amply sufficient. Starches rather than sugars should be chosen, and the protein reduction rigidly enforced, not only by excluding meat, but also by reducing articles such as milk and bread, which contain very appreciable quantities of protein, and by substituting more purely carbohydrate foods.

In certain infections of unknown origin, especially some cases of rheumatoid arthritis, great help is afforded by starvation and brisk purgation for several days, followed by a diet consisting chiefly of carbohydrate on the lines already indicated.

In cardiac failure we have to avoid throwing extra work on the alimentary canal and the liver; moreover, a plentiful supply of sugar to the blood is often a potent factor in aiding the damaged cardiac muscle. Again, in arterio-sclerotic individuals it is a manifest advantage to supply them with the food that yields sugar, rather than the proteins which call for more metabolic work and a tedious excretion of nitrogenous substances.

In cases of peptic ulcer, fluid and semi-fluid carbohydrate diets are now used extensively. The main principle, as employed in the Sippy treatment, is to give small

frequent feeds, the carbohydrate nature of which is least likely to excite gastric secretion and which will never be long delayed in the stomach. In diseases of the alimentary tract in which undernutrition is the most outstanding feature, abdominal pain and discomfort having led to curtailment of the diet, it is often essential to secure a diet which will not only sustain life, but will also help to restore the lost subcutaneous and intra-abdominal fat; and usually a high carbohydrate diet is the method of choice for securing this. Such patients are often peculiarly intolerant to fat.

In disorders of the liver, fat digestion and protein metabolism are seriously affected. Though the glycogenetic function of the liver will also be impaired, it must be remembered that the storage of glycogen is but a temporary expedient, useful for securing a steady regulation of the blood-sugar. Total extirpation of the liver in dogs has recently been shown by Mann to be followed by coma with muscular twitchings clinically comparable to the hypoglyemic convulsions produced by an overdose of insulin. From this condition they were rapidly, though temporarily, restored by the intravenous injection of glucose. Hence in acute cases of hepatic disease, high carbohydrate, especially when given in the form of glucose, is often of remarkable value. In a recent case of delayed chloroform poisoning, the administration of large quantities of glucose in solution, by mouth, produced a most dramatic recovery. For cases of acute hepatic disease such as eclampsia, acute yellow atrophy, poisoning by chloroform, arsphenamin, phosphorus, or other drugs, a plentiful supply of glucose must be attained, and this is usually easy if we give a strong solution by mouth prepared by dissolving over half a pound of glucose in a quart of boiling water in which two lemons are steeped. When cooled this makes a very palatable drink. The author has found it easy to administer, sometimes, nearly a pound of glucose a day in this manner. The administration must be spaced

out as much as possible, or else a good deal of the sugar will escape in the urine, but even here there is no danger unless the patient be a diabetic.

The renal system supplies further indications for high carbohydrate diets. When faced with a case of chronic nephritis we inquire whether this patient is affected more by an inability to excrete salts or by failure to eliminate the nitrogenous waste-products. Modern biochemical tests, such as the urea-concentration test, or the estimation of urea and non-protein nitrogen in the blood, aim at determining the capacity of the kidney for eliminating the nitrogenous waste products. When tests inform us that the capacity of the kidney for performing this function is diminished, we are immediately faced with an indication for a diet in which the carbohydrate proportion is increased and the protein reduced. One cannot but be astonished at the frequency with which patients with acute nephritis are encouraged to imbibe large quantities of milk, a diet for which, to say the least of it, there is no scientific indication in acute nephritis. Glucose is again the food for which there is a call, as it is the one which alone yields harmless end-products. In chronic cases, where there is diminished nitrogen excretion, starch rather than protein must be chosen, *i. e.*, such foods as macaroni, vermicelli, nouilles, and various substances prepared from flour, arrowroot, sago, and other starchy bodies. Many of the starchy vegetables—potatoes, carrots, artichokes, etc.—are most useful, as are also the cereal foods. In chronic cases, fresh fruit is also often invaluable, not on account of its carbohydrate content, but because it enables us to supply that measure of palatability which is very essential for the well-being of our patients. It has the further advantage of giving sufficient cellulose to maintain the bulk of the feces and so prevent constipation, and of ensuring a plentiful supply of vitamins.

LOW CARBOHYDRATE DIET

"Simple" Methods of Prescribing Diabetic Diet and Insulin. George Baehr, Herman Lande and Lulu G. Graves[1] have devised as simple a table (Table 1) as is perhaps possible, to assist the general practitioner in prescribing accurate diabetic diets without the use of mathematical formulas. In preparing this table they have modified the one of Joslin so as to make it conform to the present day needs of the high fat, low protein diets.

The twelve diets in Table 1 are called test diets, for they are designed to be used only during the first week or two, in order to eliminate the patient's glycosuria, reduce his blood sugar to a more normal level, and then test his maximum glucose burning ability. After this has been accomplished, the diet is increased in accordance with rules which will subsequently be given, this final, more adequate diet being called the permanent maintenance diet.

If the patient comes under observation with marked glycosuria but with little or no acetonuria, it is the author's practice to starve him for two days. During these two days he receives foods of only negligible food value, such as water, coffee, tea, broth, thrice-cooked vegetables (or, if these are not available, the 1 to 3 per cent. vegetables), cellu-flour bran wafers, and agar jelly, a small amount of butter and cream are allowed in order to make the foods more palatable. *A glycosuria that persists even after the fast indicates the necessity for the use of insulin.*

If the urine has become free of sugar before the end of the preliminary forty-eight hour fast, and little or no acetone has appeared, the case may be considered of only moderate severity. One can then, with confidence, skip the first three test diets and begin with Diet 4, which contains 30 gm. of carbohydrate. If the patient weighs

(1) Jour. Amer. Med. Ass'n., May 10, 1924.

Diet No.	Carbohydrate	Protein	Fat	Calories (Approximately)	Carbohydrate: 1-3% Vegetables	3-5% Vegetables	10% Vegetables	15% Vegetables	Orange	Apple	Bread	Uneeda	Potato	Oatmeal	Protein and Fat: Eggs	Meat, Fish	Cheese	Cream 20% Fat	Butter	Olive Oil
1	15	40	120	1,300	200	100	...	...	...	...	..	..	...	...	2	70	20	150	60	10
2	20	40	120	1,320	200	200	...	...	...	...	..	..	...	...	2	70	20	150	60	10
3	25	40	120	1,340	200	200	...	...	50	...	..	..	...	...	2	70	20	150	60	10
4	30	40	120	1,360	200	200	...	...	100	...	..	..	...	...	2	70	20	150	60	10
5	40	40	120	1,400	200	200	...	...	100	...	..	2	...	...	2	70	20	150	60	10
6	50	40	115	1,400	100	200	150	...	100	...	..	2	...	...	2	70	20	150	55	10
7	60	40	110	1,400	100	200	150	...	100	...	20	2	...	...	2	70	..	150	55	10
8	75	40	110	1,450	100	200	150	...	100	100	20	2	...	...	2	70	..	150	55	10
9	100	40	100	1,460	100	100	150	100	100	100	20	2	100	...	2	70	..	100	55	10
10	125	40	90	1,470	100	100	150	100	100	100	40	2	200	...	2	70	..	100	45	10
11	150	40	80	1,480	100	100	150	100	200	100	60	3	200	...	1	70	..	100	45	..
12	200	40	60	1,500	100	100	150	100	200	200	80	3	200	200	1	70	..	100	45	..

Corrections for Body Weight (Adults Only)

35 to 40 kg. (75 to 90 pounds) — 25 per cent.
40 to 50 kg. (90 to 110 pounds) — 20 per cent.
50 to 55 kg. (110 to 120 pounds — 10 per cent.
65 to 70 kg. (140 to 155 pounds) + 10 per cent.
70 to 80 kg. (155 to 175 pounds) + 20 per cent.
80 to 90 kg. (175 to 200 pounds) + 25 per cent.

For permanent maintenance diet, increase the amount of protein by ½ and the fat by ¼

Table 1.—Diabetic test diets for persons weighing from 55 to 65 kg. (120 to 140 pounds). Protein, 2/3 gram per kilogram of weight. Carbohydrate begins with minimum amount on which the ketogenic ratio might be preserved in an individual of this weight and calory requirement while at rest. The total calories are from 20 to 25 per cent. below the average requirements for individuals of this weight while at rest.

less than 120 pounds (55 kg.) or more than 140 pounds (65 kg.), all the figures for Diet 4 must be appropriately corrected according to the corrections listed at the foot of the table.

On the following day, Diet 5 is given and the diet increased daily thereafter until glycosuria first recurs. Or, if the patient is judged to have an exceedingly mild case because of the rapidity with which the urine becames sugar-free on fasting, time may be further saved by skipping alternate diets. Diet 4 should then be followed by Diets 6, 8 and 10. When there is doubt as to the severity of the disease, the alternate, odd-numbered diets should not be skipped. On the very first day that the glycosuria recurs (or the blood sugar begins to rise), the test diets should be stopped and a twenty-four hour fast again instituted. This completes the test, and the patient is ready to be placed on his permanent maintenance diet, which is the diet two numbers above the one on which the glycosuria first reappeared. But it is now necessary to increase the protein allowance of this diet by one half and the fat allowance by one fourth, in order to supply an adequate permanent protein allowance (1 gm. for each kilogram of body weight) and a sufficient number of calories to prevent undue loss in weight.

In writing the menus for the patient, the main point to remember is that the food, and especially the carbohydrate food, must be distributed as equally as possible into the three meals.

If undue loss in weight should occur on a permanent maintenance diet, in spite of the fact that the urine continues free of sugar and of acetone and the blood sugar level remains low, the fat allowance may be increased 20 or more grams.

Elliott P. Joslin[2] maintains that the treatment of diabetes has become "extraordinarily simple". The

(2) New York State Jour. Med., October, 1923.

controversy between "high fat and low fat" advocates he would settle as follows:

Patients coming for treatment should be regarded as mild until proved otherwise.

They should be given a chance to show whether their disease is of slight intensity or of moderate intensity before they are subjected to the treatment of the severest type of diabetes.

The severest possible diabetic may be justly condemned to a formula by which he can secure the largest possible amount of fat for the smallest possible amount of carbohydrate with which to avoid acidosis, but the mildest diabetic should not be sentenced to this ration, but be given the largest quantity of carbohydrate compatible with a constantly normal blood sugar and normal urine and then the question of acidosis will not rise above the horizon.

"Elaborate formulas for the arrangement of the diabetic diet are unnecessary. Any patient who can keep sugar-free with one gram of protein per kilogram body weight can safely have three grams of fat for each gram of carbohydrate in his diet if he requires it, though a lower fat carbohydrate ratio is to be preferred. If the carbohydrate must be kept so low that he cannot keep sugar-free and maintain strength and weight, then he needs more calories, and the only safe way to give more calories is to lower the protein still further, namely, to ⅔ gram per kilogram body weight, when the fat can be raised without harm to as much as four grams for each gram of carbohydrate which the urine of the patient shows that he tolerates. This is the whole sum and substance of the modern treatment of diabetes".

Acquaintance with the values of carbohydrate, protein, and fat in the meager menu of the diabetic is essential for doctor and patient[3]. (See Table 2.) For diet-

(3) Cards with Joslin's Diabetic Diet can be obtained from Thos. Groom Co., Boston.

etic treatment alone it is advantageous for the patient to be able to test his urine for sugar, but if insulin is to be used this is absolutely essential.

The use of insulin by the general practitioner in diabetes is nearly as simple. Patients coming with sugar in the urine are given one unit of insulin 30 to 15 minutes before their first meal. That meal is made up from one of four test diets which is nearest to the entire daily diet the patient has been taking. This diet is continued until the next morning, when one advances to the next test diet of lesser food value. Before the second meal the patient receives two units, before the third meal three units, before the fourth meal four units, and before the fifth meal five units; and thereafter five units before each meal. Along with the increase in insulin one progresses daily to test diets of lesser food value. So soon as the patient is sugar-free, which usually results within 36 to 72 hours, one simply trades over to a maintenance diet with a similar quantity of carbohydrate, but with more protein and fat and thereafter proceeds day by day until sufficient calories are obtained. Coincidentally, the insulin is increased or decreased gradually according to whether sugar shows or is absent from the urine, and according to one's ideas as to the amount of carbohydrate the patient should receive. Little by little the noon dose is abolished and usually within two weeks the patient can be sent home, having been instructed about the continuance of treatment with its possibilities for good or harm.

There is nothing obscure about the dosage of insulin any more than there is anything obscure about the amount of gasoline it takes to run an automobile. With some patients one unit will accomplish a great deal, but with others less, just as one gallon will yield twenty miles to one automobile and but ten miles to another.

Hypoglycemic reactions have been rare with the treatment outlined. Those that occurred yielded quickly to

the juice of an orange. With insulin the tolerance for carbohydrate can be increased, but whether this increase of tolerance is wholly dependent upon the amount of insulin given or upon a reactivation of the islands in the pancreas is not yet definitely known. There is some indication to believe that the pancreas regains a portion of its function which seemed to be lost.

TABLE 2—*Dietetic Values of Food Commonly Used by Diabetics*

Water, clear broths, coffee, tea, cocoa shells and cracked cocoa can be taken without allowance for food content.

Foods arranged approximately according to content of carbohydrates.

	5%		10% *	15%	20%
* Reckon average carbohydrate in veg. as 3%—of 10% veg. as 6%					
VEGETABLES (fresh or canned)	1%-3%	3%-5%	10%	15%	20%
	Lettuce	Tomatoes	Str. Beans	Green Peas	Potatoes
	Cucumbers	Brussels Sprouts	Pumpkin	Artichokes	Shell Beans
	Spinach	Water Cress	Turnip	Parsnips	Baked Beans
	Asparagus	Sea Kale	Kohl-Rabi	Canned Lima Beans	Green Corn
	Rhubarb	Okra	Squash		Boiled Rice
	Endive	Cauliflower	Beets		Boiled Macaroni
	Marrow	Egg Plant	Carrots		
	Sorrel	Cabbage	Onions		
	Sauerkraut	Radishes	Green Peas canned		
	Beet Greens	Leeks			
	Dandelions	String Beans canned	Strawberr's	Raspberries	Plums
	Swiss Chard	Broccoli	Lemons	Currants	Bananas
	Celery	Artichokes	Cranberries	Apricots	Prunes
	Mushrooms		Peaches	Pears	
FRUITS	Ripe Olives (20% fat)		Pineapple	Apples	
	Grape Fruit		Blackberr's	Blueberries	
			Oranges	Cherries	

1 gram protein.....4 calories
1 gram carbohydrate..4 calories
1 gram fat.....9 calories
6.25 grams protein contains 1 g. nitrogen

1 kilogram=2.2 pounds
30 grams g. or cubic centimeters c.c=1 ounce
A patient "at rest" requires 25 calories per kilogram

30 Grams 1 Oz. Contain Approximately	Carbohydrates G.	Protein G.	Fat G.	Calories
Vegetables 5%	1	0.5	0	6
Vegetables 10%	2	0.5	0	10
Shredded Wheat	23	3	0	104
Uneedas, two	10	1	1	53
Potato	6	1	0	28
Bread	18	3	0	84
Oatmeal, dry wgt.	20	5	2	118
Oysters, six	4	6	1	49
Milk	1.5	1	1	19
Meat (cooked, lean)	0	8	5	77
Fish	0	6	0	24
Chicken (cooked, lean)	0	8	3	59
Egg (one)	0	6	6	78
Cheese	0	8	11	131
Bacon	0	5	15	155
Cream, 20%	1	1	6	62
Cream, 40%	1	1	12	116
Butter	0	0	25	225
Oil	0	0	30	270

Intarvin

Intarvin Fat—Glyceryl Margarate—of Slight Value in Diabetes Mellitus. The study of the fate of fatty acids in the diabetic organism, especially their ability to produce ketone substances, began with the work of Baer and Blum (1906), who were able to show that the administration of salts of butyric acid and isovaleric acid to a diabetic led to an increased excretion of ketone bodies, whereas propionic and normal valeric acid did not. Later, (1912) A. I. Ringer showed that by feeding phloridzinized frogs fatty acids with an even number of carbon atoms (butyric, caproic, etc.) the ketone substances excreted in the urine were increased. On the other hand, feeding propionic acid or other acids with an uneven number of carbon atoms led to no increase in ketone substances, but rather an increase in glucose formation. Ringer stated at this time that the higher fatty acids, that is, the acids with fifteen or seventeen carbon atoms, might be of value in the treatment of diabetes mellitus, since they could not give rise to acids

with an even number of carbon atoms and since, in every case in which glucogenesis took place, there was a coincident decrease in the amount of ketones excreted in the urine. However, the feeding of the higher fatty acids with an uneven number of carbon atoms, such as margaric acid, to diabetic individuals had never been tried very extensively on account of the difficulty of procuring such acids in sufficient quantities, in a pure enough state, and in a palatable form. Ringer found that the glycerol ester of margaric acid was distasteful and that patients became nauseated after taking it. He abandoned its use on this account.

More recently (1923) this fatty acid was prepared by Kahn and Nolan, and the substance called "Intarvin Fat." Kahn states that 90 per cent. of the intarvin fed is absorbed from the gastro-intestinal tract and catabolized without the production of ketosis. He has used it in the treatment of diabetics and has given it to normal fasting individuals who had ketone bodies in their urine. The feeding of intarvin in both diabetic individuals and in normal individuals with a starvation ketosis has resulted in the prompt disappearance of ketone bodies from the urine.

In 4 patients studied by Chester S. Keefer, Wm. A. Perlzweig and Wm. S. McCann[4] at Johns Hopkins Hospital, there was a very definite diminution in the amount of acetone bodies excreted in the urine during the day on which the intarvin was fed, with the exception of one patient in whom there was a rise of acetone body excretion. In view of these results it is probable, but not certain, that intarvin gives rise to less ketosis than does an equivalent amount of ordinary fat. From a practical standpoint the use of intarvin fat in diabetes has not been found to be of any great value because it is intensely disagreeable to patients to whom it is given as the chief source of fat. Nearly everyone of the patients complained of the bad after taste of the fat and one

(4) Bull. Johns Hopkins Hosp., September, 1924.

patient could not tolerate it at all. He became nauseated and vomited after eating it. Nausea was experienced by several of the patients. All were unwilling to repeat the experiment.

Sevringhaus (1923) reported that normal individuals absorbed 96.5 to 96.8 per cent. of the glyceryl margarate ingested when it is given with diets low in fat, but that it had little or no anti-ketogenic value. On the other hand, Benedict and West (1924) found that there was no rise of acetone bodies or organic acids in the urine during the period of intarvin administration.

Meat Diet

Carnivores' Diet in the Treatment of Flagellate. Diarrhea. Robert W. Hegner,[5] acting on the suggestion obtained from a survey of literature that intestinal protozoa have been reported from carnivorous mammals but very rarely; that they are not so rare in omniverous mammals; but often present in herbivorous mammals in great abundance, studied three rats that had been fed on a well balanced carnivores' diet throughout their lives (174 days.) These were found to be free from giardias and trichomonads, whereas other rats from the same colony, that were fed largely on a carbohydrate diet, were abundantly infected with these protozoa. Of fifteen rats that were fed on a carnivores' diet for one week, 7 per cent. lost their giardias, 7 per cent. lost their trichomanads, the remaining 93 per cent. lost on the average 90 per cent. of their giardias, and 98.2 per cent. of their trichomonads.

These observations and experiments on mammals suggest that a carnivores' diet might be of use in ridding man of intestinal protozoa. His clinical experience is limited to one case of trichomonas and two of giardia infection. The patient with trichomonas infection had suffered from diarrhea for years. The stools were watery

(5) Jour. Amer. Med. Ass'n., July 5, 1924.

and were swarming with trichomonads. Three days after beginning the meat diet, the patient began to pass formed stools in which no flagellates could be found, and he was feeling much better. Thirty-two days later this patient was feeling very well, was having no diarrhea, and the stools were still free from flagellates.

The giardia cases have not responded to the meat diet so quickly and definitely. The number of stools decreased, many of them were formed and the patients improved in health.

Low Protein Diet

Diet in Nephritis. In nephritis the body has more or less difficulty in handling water, salt, and nitrogen. We know that if we give much water or salt these substances will be retained and the swelling increased in the edematous types of the disease. In the hypertensive case we are certain that too much protein intake will be followed by an accumulation of nitrogen in the blood. If this is so, why do we not make use of these facts in treating our nephritic patients? Why force 3000 c.c. of fluid on kidneys that can hardly handle 600 c.c.? Why give 100 gm. of protein when the patient can take care of only 40 gm.? Why give 6 gm. of salt when 4 gm. of it is going to be retained?

Hence, in prescribing diets for nephritic patients, we must think of quantities. This is not at all difficult with the use of a diet sheet similar to the one reproduced here.

The foods are divided into three groups according to the amount of protein in them. In group 3, there is so little protein that one can ordinarily ignore it. In group 1, each full portion (indicated to the right of each foodstuff) contains approximately 4 gm. of protein. In group 2, each full portion contains approximately 8 gm. of protein. To make it still simpler, we avoid mentioning grams and instruct the patient that each full portion in Group 1 counts one point. In Group 2, it counts two

points. The number of points for the day is inserted in the blank space left for that purpose at the top of the sheet. A low protein diet would be represented by seven points (28 gms.). A very generous protein diet—for a nephritic patient—would be equivalent to fifteen points (60 gm.). Another blank line for the prescription of the amount of fluid is placed immediately under the prescription of protein. The physician may use his own discretion about allowing tea or coffee or substitutes for those. The patients are not allowed to add salt to the food after it comes to the table. The average patient under this regimen does not get more than 4 or 5 gm. of salt a day. It he is edematous, we can still further decrease the salt by ordering fresh butter, salt-poor bread, vegetables, meats, etc., boiled free from salt; and, if necessary, the use of distilled water, whenever water is used in the diet. The former method reduces the salt intake approximately 2.0 gm. a day, and the latter to perhaps as low as 0.5 gm. a day.

NEPHRITIS DIET

Any combination of the foods listed below may be selected.
Foods not listed below must not be taken.
In Groups 1 and 2 there is a restriction in the total amount.
The foods in these groups must be served in full or half portions.
A full portion in Group 1 counts 1.
A full portion in Group 2 counts 2.
In Group 3, the quantity of each is not restricted, although you are urged to use discretion.
Points on recipes to count as indicated.
YOUR TOTAL SCORE FOR THE DAY SHOULD BE.....
YOUR TOTAL AMOUNT OF FLUID SHOULD BE.....PINTS.
Do not add salt or spices to the food after it has been cooked.

GROUP 1

(Each full portion counts 1)

	Full Portion
Bread (White)	1 av. slice
Bread (graham)	1 av. slice
Uneeda biscuit	5 crackers
Shredded wheat	1 biscuit
Graham crackers	5 crackers
Cereals, Etc.	
Oatmeal	2 tbsp.*
Boiled rice	3 tbsp.
Cornmeal mush	4 tbsp.
Cream of wheat	6 tbsp.
Farina	6 tbsp.
Macaroni	4½ tbsp.

Vegetables, etc.	*Full Portion*
Baked beans	1 tbsp.
Lima beans	1½ tbsp.
Potato, creamed	1 tbsp.
Potato, mashed	1½ tbsp.
Potato, baked	1½ med.
Potato, boiled	1½ med.
Canned-corn	2½ tbsp.
Green peas	2 tbsp.
Beets	5 tbsp.
Spinach	4 tbsp.
Bananas	2 large
Cream, heavy	2/3 cup

GROUP 2

(Each full portion counts 2)

	Full Portion	*Fish*	*Full Portion*
Milk	1 glass	Cod, boiled	1″ x 1″ x 1½″
Egg	1 egg	Haddock, boiled	1″ x 1″ x 1½″
Eggs (scrambled)	1½ tbsp.	Halibut, boiled	1″ x 1″ x 1½″
Flour, sifted	2-3 cup	Mackerel, boiled	1″ x 1″ x 1½″
Meats		Salmon, boiled	1″ x 1″ x 1½″
Lamb chop, broiled	2-3 chop	Smelt	½″ x 1″ x 3″
Lamb, roast	3″ x 2½″ x ¼″	Oysters	7 oysters
Beef, roast	3″ x 2″ x ¼″	Crabmeat, canned	2 tbsp.
Beef steak, broiled	2″ x 1″ x 1″	Salmon, canned	1½ tbsp.
Chicken, roast	3″ x 3″ x ⅛″	Shrimp, canned	6 small

GROUP 3

(No restriction)

Vegetables	*Fruit*	*Miscellaneous*
Asparagus	Apple	Sugar
Cabbage	Apricot	Maple sugar
Carrots	Blueberries	Syrup
Cauliflower	Cherries	Honey
Celery	Cranberries	Candy
Cucumbers	Grapefruit	4 dates a day
Lettuce	Grapes	3 Sunshine arrowroot cookies a day
Mushrooms	Muskmelon	Cornstarch
String beans	Lemons	Arrowroot
Tomato (fresh)	Oranges	Tapioca
Tomato (cooked)	Peaches	Post-toasties
Onions	Pears	Butter
Squash	Pineapple	Olive-oil
Turnips	Plums	
	Prunes	
	Raspberries	
	Strawberries	
	Watermelon	

*All tablespoonfuls are "rounded."

The advantages of this nephritis diet sheet are three:

1. It is so simple that any one of any intelligence can follow it anywhere.

2. It restricts the patient's intake of protein, water, and salt to the amounts desired by the physician.

3. It gives the patient great freedom of choice in the selection of his menu.

Fruit Diet

Raw Fruit Diet. F. Mendel* reports favorable results with raw fruit diet in cardiac or renal edema where different preparations of digitalis, without strict diet, were ineffective. Three days of raw fruit, 1 kg. daily, led to remarkable improvement. One kg. of raw

(*) Klin. Wochenschr., Apr. 8, 1924.

fruit daily suffices to counteract the sensation of hunger and thirst and gives sufficient nourishment, about 600 calories, to avoid exhaustion, especially when patients stay in bed.

Gastric Rest Diet

Gastric Rest Cure in Peptic Ulcer. Warren Coleman[6] has devised a gastric rest treatment which has been in continuous use for twelve years, and given satisfactory results. In this diet, glucose-salt enemas are given throughout; and, for the first three to five days, only water is allowed by mouth. Feeding by mouth is started on the fourth to the sixth day. The only foods permitted are olive oil or butter fat and white of egg. Later in the treatment, yolk of egg and cream may be added to the diet in replacement of a portion of the other fats.

The sources of injury to the peptic ulcer may be grouped as chemical and mechanical. Both kinds of injuries are incident to the digestive activities of the stomach. The problem, therefore, becomes one of selecting foods which do not excite the gastric secretion and which least stimulate the motor activity of the organ. Pawlow has demonstrated that such foods exist.

Fats not only are not digested in the stomach, but, when taken with other foodstuffs, diminish or delay the gastric secretion. They are capable even of inhibiting the powerful psychic impulse. Fats leave the stomach slowly, and thus form a protective coating over the ulcer. The most suitable fats for the ulcer diet are olive oil and butter fat. The butter should be fresh and unsalted; if there is any probability of its containing more than a trace of butyric acid, the butter should be washed several times in water, since butyric acid is a powerful excitant of gastric secretion. Yolk of egg and cream are less desirable forms of fat because both contain protein; but experience has shown that they

(6) Jour. Amer. Med. Ass'n., Sep. 20, 1924.

may be used late in the treatment without causing a return of symptoms. Fat must be depended on to furnish the greater portion of the energy of the diet.

White of egg, when given alone, or with a small quantity of water, or lightly boiled, does not excite the gastric secretion. It is digested in the stomach only when gastric digestion has been initiated by some other food or by the psychic impulse, and passes quickly into the duodenum. White of egg may therefore be selected to furnish the protein of the ulcer diet. The amount of nitrogen need only slightly exceed the nitrogen minimum, that is, from 3 to 5 gm. a day. This amount is provided by the whites of from six to eight eggs.

As so-called carbohydrate foods, the cereals, are mixtures of starch and protein their digestion is difficult and prolonged, and as pure carbohydrates, such as the sugars, are apt to undergo fermentation in the stomach, it is desirable to give no carbohydrates by mouth, but to give glucose by rectum. Glucose is readily absorbed from the large intestine, but it has been found expedient to give not more than from 90 to 100 gm. a day. Sodium chlorid is added to the glucose enemas to prevent loss of chlorid from the body.

The greater portion of the water required may be given by rectum. If thirst is not controlled by the enemas, moderate quantities of water may be allowed by mouth whenever desired. Water excites the gastric secretions only when given in large amounts at a time.

Based on the foregoing considerations, the following regimen is recommended:

The patient is put to bed to minimize the effect of exercise on gastric motility, to lower his metabolism, and to assist in retaining the enemas. For from three to five days, depending on the ability of the patient to withstand partial starvation, no food whatever is given by mouth. If thirst is not controlled by the enemas, small quantities of water, from 1 to 3 ounces (from 30 to 90 c.c.) at room temperature, or warmed, may be

allowed whenever desired. Cracked ice may be held in the mouth unless the water that is swallowed provokes pyloric spasm.

The glucose enemas are begun on the first day of treatment. They consist of glucose 30 gm. in 300 c.c. of physiologic sodium chlorid solution. Each morning, before the first nutrient enema, the rectum and sigmoid should be emptied by an enema of soap-suds or sodium chlorid solution (0.7 per cent.). The glucose solution is given hot, from a vacuum bottle, by the drip method at a rate that consumes from half to three quarters of an hour. Three or four such enemas are given daily, equally spaced throughout the sixteen waking hours. When cramps occur, the strength of the solution must be reduced, or the number of enemas restricted. The enemas are continued throughout the treatment.

On the fourth to the sixth day, feeding by mouth is begun. The only foods permitted are white of egg and olive oil or butter fat. The schedule of feedings should be so arranged that the white of egg and fat are given at different hours, to prevent the delay that fat causes in the passage of the albumin from the stomach. The intervals between the feedings should be made as long as may be feasible. They should not be less than two hours. The total quantity of food should be increased as rapidly as the stomach can take care of it in order to control the loss of weight. The total amount given at any feeding need never exceed 90 gm.

For practical reasons, olive oil is the fat of choice for the average patient. From 45 to 75 c.c. may be given the first day. It should be given clear; it is taken more easily when it is chilled. The whites of from three to four eggs may be given the first day, thoroughly mixed with a small quantity of water, or whipped to a foam, or lightly coddled. If desired, the white of egg may be prepared differently for each feeding; a pinch of salt may be added. As treatment pro-

gresses, the quantity of oil is increased to a maximum of 150 c.c., and the whites of egg to a total of six or eight.

With some patients, olive oil palls on the taste, and much or all of it must be replaced by some other fat. In such instances, unsalted butter may be employed in corresponding amounts. Unless perfectly fresh, the butter should be washed in water several times to remove any butyric acid that may be present. The butter may be given melted or cold, and a pinch of salt may be added before taking.

For the sake of variety, yolk of egg may substituted for a portion of the olive oil or butter fat in the proportion of one yolk to about one teaspoonful of the oil or butter. The yolk and the white of egg should not be given together. The yolk may be heated through, but should not be cooked hard. A little sweet butter and salt may be added.

Occasionally, a patient will rebel against all the fats mentioned, and cream must be substituted for them. Of cream 690 c.c. is required to replace 150 c.c. of olive oil. But cream is not as desirable as olive oil and butter fat because it calls forth a weak gastric secretion, and is not capable of exerting the same demulcent action on the raw surface of the ulcer.

This diet should be continued for from three to four weeks, and, as after other diet cures, only specially selected foods should be allowed for many months.

All patients lose weight in the earlier part of the treatment. Usually, the lost weight is recovered before the patient is ready to leave the bed. If the loss of weight in any patient appears dangerously rapid, the diet should at once be modified by the addition of suitable quantities of cream and whole eggs to prevent further loss. Gastric distress quickly subsides after treatment is begun. It may disappear on the first day, and is nearly always gone by the third day.

BACTERIOTHERAPY

Acidophilus Milk. Rettger and Cheplin and their coworkers have shown, by well controlled experimentation, that by the use of preparations containing a large number of *Bacillus acidophilus* the human intestinal flora could be markedly simplified; that it could be changed from a preponderatingly Gram negative to a preponderatingly Gram positive type, and that gas producing and putrefactive organisms could be almost completely stamped out or replaced by the *Bacillus acidophilus*. They have also shown that this transformation or simplification of the intestinal flora could be accomplished by the ingestion of large amounts of glucose and lactose, these sugars apparently furnishing the necessary pabulum for the growth of the *Bacillus acidophilus* normally present in small numbers in the human intestine. This work indicated, however, that in order to accomplish this result, impracticably large amounts of these sugars—between two hundred and four hundred grams—were required each day. They have also shown that the same change in flora might be accomplished by the ingestion of large amounts of whey broth cultures, or by a combination of the latter with the sugars mentioned above. A third way in which the same result could be accomplished was by the ingestion of milk cultures of the organism, either alone, or better, in combination with lactose in amounts usable clinically.

William Earl Clark and Matthew White Perry[7] report observations on 84 adult patients who have taken a quart of milk each day for a period of six weeks. The patients used with the daily quart of milk 75 grams of lactose. This has seemed a valuable addition, enabling the change in flora to occur much more rapidly and effectively, and enhancing the clinical value of the preparation. At the end of six weeks' treatment all patients were advised

(7) New York Med. Jour. and Med. Rec., Dec. 19, 1923.

to continue the use of lactose, and to date the majority have continued to do so. The author's experience is that the continuation of this sugar maintains the new flora and the beneficial results obtained. On stopping the lactose there is a rapid reversal to the original type of flora.

In the treatment of chronic constipation acidophilus milk with lactose has a distinctly laxative quality. The milk alone did not show such an effect. The general tendency was toward a gain in weight. Of the group using the milk and lactose, sixteen were able to discontinue all laxatives; the remainder found it necessary to use mineral oil or agar, preparations milder than they had hitherto used.

Patients who seemed to be especially benefited were those who complained particularly of an excess of intestinal gas, of flatulence, and of the passage of large amounts of gas by rectum. Of 27 such cases 23 reported marked improvement and four noted no effect. In this group 24 out of the 27 were on the average below weight, and again the general tendency was toward a gain.

Five patients, all elderly individuals between 60 and 70 years of age, in whom the findings were those of chronic myocardial weakness, presented themselves because of intestinal gas and bloating. At times the abdominal distention was so great as to seem to embarrass further the already greatly embarrassed circulation. Relief from the digestive disturbances in these cases was marked in all five.

Six cases of chronic enterocolitis of average duration of eighteen months made a rapid recovery under this treatment combined with rest in bed and a diet deficient in roughage, and have remained well at the end of one year. In an additional chronic case, where achylia gastrica existed, no benefit was experienced from the use of the milk and lactose.

Of four cases of chronic eczema that had not yielded to usual treatment, three recovered and one did not improve.

Nicholas Kopeloff[8] reports a series of thirty constipated subjects under observation before, during and after treatment with *B. acidophilus*. A comparison of these periods shows that during treatment the number of normal defecations was significantly increased. The beneficial influence of *B. acidophilus* usually persists for a considerable period of time after treatment has been stopped. Patients have been observed for from one week to about one year after treatment, and almost without exception all have more normal defacations after than before treatment. The use of lactose during and after ingestion of *B. acidophilus* does much to enhance the beneficial effects. A transformation of the intestinal flora from a proteolytic to an aciduric type, as shown by microscopic and plate counts, may generally be induced. Such transformation is usually accompanied by almost daily defecations regardless of the severity of the constipation. Two cases of diarrhea have also been successfully treated by the ingestion of *B. acidophilus*.

To study the mode of action of *bacillus acidophilus* therapy, Nicholas Kopeloff and Philip Beerman[9] conducted the following experiments:

1. *B. acidophilus* milk was centrifuged and run through a Mandler diatomaceous filter. Thus the chemical constituents were little altered. When fed to constipated patients it was practically without effect. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

2. *B. acidophilus* milk was sterilized and lactic acid added, thus again approximating the original chemical composition. When fed to constipated patients, little

(8) Archiv. of Int. Med., Jan. 15, 1924.
(9) Ibid.

change was noted. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations.

These data indicate that *B. acidophilus therapy is essentially bacteriologic rather than physical or chemical in nature.*

C. C. Bass and W. E. Jones[1] advise that, to get the best results, a glass of acidophilus milk be taken with each meal so as to inoculate the food heavily with viable bacilli.

ENDOCRINE THERAPY

In General

The Limitations of Organotherapy. These limitations are well set forth by A. J. Carlson[2]. If we define organotherapy as the partial or complete control of disease due to hypofunction of an organ by administration of substances prepared from this organ, this field of therapy can at present be credited with only two distinct successes, *i. e.,* thyroid and insulin in hypothyroidism and pancreatic diabetes respectively. If we accept for our guidance the following two principles: (1) that it seems irrational to expect any remedial effect against disturbances of organs that do not demonstrably produce some chemical regulator or hormone and (2) that there is little or no hope for successful organotherapy in diseases due to a primary hyperfunction of organs, our patient will not only be spared useless expenditures of money but also saved from the positive dangers of anaphylactic shock, protein sensitization, toxicity and localized tissue damage inherent in the injection of some of these organ extracts of complex and dubious composition.

(1) New Orleans Med. and Surg. Jour., September, 1923.
(2) Jour. Amer. Med. Ass'n., Mar. 29, 1924.

Effect of Drugs on Basal Metabolism. In view of the clinical importance which the estimation of basal metabolism has assumed, the question what effects the usual remedies have upon the basal metabolic rate may arise. W. M. Boothby and L. G. Rowntree[3] have studied twenty-five commonly used drugs including acetylsalicylic acid, barbital, caffein, cinchophen, codein, iodids, morphin, radium water, strychnin, sulphonmethan. These in single, moderate doses do not demonstrably influence the basal metabolic rate. On the other hand, *in the clinical estimation of the basal metabolic rate, neither epinephrin nor insulin should be given within several hours preceding the test, nor thyroid within several weeks.* The administration of iodids does not affect the metabolism of a normal individual, but may convert a case of adenomatous goiter without hyperthyroidism into one with hyperthyroidism. The increased metabolism so produced represents the intensity of the new syndrome.

R. Schoen[4] finds that, although morphin depresses the basal metabolism to as much as 25 per cent. in some cases, after repeated doses this depression of metabolism no longer takes place.

Insulin

The discovery of insulin has advanced us one step—but only one step—in the direction of an understanding of and the cure of diabetes mellitus. We know that insulin is not a specific cure for diabetes; and that, under its use a limited recovery of food tolerance may take place, but that, in the large majority of cases, the benefit persists only so long as the injections are continued.

A great deal of work has been done to elucidate the mode of action of insulin; and—as is so often the case in nature—the deeper the problem is investigated the

(3) Jour. Pharm. and Exper. Therap., September, 1923.
(4) Arch. Exper. Pathol and Pharm., May, 1924.

more complex it becomes. Insulin has neither simplified the treatment nor our understanding of the nature of diabetes mellitus.

Mode of Action of Insulin. P. J. Cammidge[5] insists that diabetes may arise from other causes than pancreatitis even if we agree to define diabetes as a condition in which defects of metabolism are associated with insufficiency of the internal secretion of the pancreas. We must distinguish between relative pancreatic deficiency dependent on an inability of a normal pancreas to produce a sufficiency of its internal secretion to counteract completely the excessive activity of opposing influences promoting glycogenolysis, and the absolute form due to functional or organic defects in the gland; though he admits that relative pancreatic deficiency may become absolute in the course of time, and a deficiency that was only functional in the first instance may give rise to organic changes if the metabolic disturbance is allowed to continue unchecked. By an analytic method devised by him, Cammidge finds that about 38 per cent. of unselected series of cases showed evidence of an absolute deficiency of the internal secretion of the pancreas; in 32 per cent. there was a relative deficiency associated with excessive activity of one or the other of the factors known to promote glycogenolysis, while in the remainder there were no indications of any pancreatic defect. When, however, only cases of a severe type were considered, absolute deficiency of the internal secretion of the pancreas was found in more than 80 per cent., although previous examinations in some had revealed merely a relative defect. Conversely, observations on the effect of treatment have demonstrated that an absolute pancreatic deficiency often becomes relative as the condition of the patient improves, and reverts to its original type if dietetic control is abandoned. In some

(5) Jour. Amer. Med. Ass'n., Nov. 1, 1924.

patients, however, an absolute deficiency persists in spite of suitable treatment, probably owing to there being irreparable damage of the pancreas.

The results of metabolic experiments suggest that insulin has two functions: (1) as a promoter of glycogenesis and (2) as an activator of sugar utilization by the tissues, and that these are dependent on separate and distinct fractions; for, in a series of observations on guinea-pigs and rats, it was found that, although insulin given by the mouth had no effect on the sugar content of the blood or the respiratory quotient, it was capable of preventing the glycogenolysis caused by epinephrin injected subcutaneously. Such a finding can be most reasonably interpreted on the assumption that insulin is so modified in the alimentary tract; or during absorption, that a fraction on which the utilization of sugar depends is either destroyed or not absorbed, while another fraction possessing antiglycogenolytic properties passes into the circulation unchanged.

1. *The fact that glycogen is deposited in the liver of a depancreatized animal when the sugar content of the blood is reduced to the physiologic level by insulin injections is incontrovertible.* The experiments of Howard and Cammidge have shown that the amount of sugar formed from soluble starch or glycogen by the isolated diastatic ferment of the liver is reduced by the addition of insulin according to the concentration employed, but that the addition of insulin alone is effective only if the reaction of the medium is acid or neutral. If, however, parathyroid also is added, a similar reduction occurs in alkaline range and is particularly pronounced at the normal reaction of the blood. It would therefore seem probable that the internal secretion of the parathyroids bears much the same relation to insulin as Langfeldt's (1921) experiments showed thyroidin does to epinephrin functioning as an activator at the reaction of the blood. Since then L. B. Winter and W.

Smith[6] have shown that the injection of parathyroid along with insulin, into rabbits, materially enhances the action of the latter. Seeing that the thyroid-epinephrin combination promotes the breaking down of glycogen into sugar by the diastatic ferment of the liver, and that a combination of parathyroid and insulin has an opposite effect, it is tempting to assume that the rate of glycogenolysis in the liver is determined, in part at least, by the balance existing between the two systems at any particular time. The activity of the isolated diastatic ferment of the liver can be controlled at will by suitably adjusting the concentration of the added hormones. Lyman Nicholls and M'Cann found that injections of insulin and epinephrin had opposite effects on the blood sugar, the net result of simultaneous injections being the algebraic sum of the two factors. While pituitary extract has no direct influence on the activity of the diastatic ferment of the liver it possesses the property of preventing the depressing effect of insulin on glycogenolysis, even in the presence of parathyroid; thus confirming the conclusion arrived at by Burn as a consequence of his observations on injected animals, which suggested that there is an antagonism between the hormone of the posterior lobe of the pituitary gland and insulin differing fundamentally in its nature from that existing between epinephrin and insulin. The existence of such a direct antagonism is interesting in view of the relation of the pituitary gland to the central nervous system, and it may possibly account for the absence of glycogen from the latter, and also explain why the brain and liver are provided with a special nervous connection.

2. It has been held by some that the fundamental defect in diabetes is an inability of the tissues to utilize carbohydrate, and that this defect in the normal balance between supply and demand is the cause of the hyper-

(6) Jour. Physiol., October, 1923.

glycemia; whereas others have maintained that an overloading of the blood with sugar, due to excessive production, is the essential factor. Those who have adopted the former view have based their opinion largely on the evidence furnished by observations on the respiratory quotient, which Benedict and Joslin found was lowered as the severity of the disease increased, thus indicating an impairment or loss of power of the organism to utilize sugar. Recently, more direct proof of faulty utilization of sugar by the muscles and general tissues in severe cases has been provided by Lawrence,[7] who showed that the difference between the sugar concentration in the arterial and venous blood of a limb is much less in advanced diabetes than in health. Moreover, as he found that the difference increased and approximated to the normal after the administration of insulin, and as other observers have reported a rise in the respiratory quotient, it may be inferred that the loss of power to utilize sugar in such cases is dependent on a deficiency of the internal secretion of the pancreas.

It does not follow, however, that the hyperglycemia is due entirely to the inability of the tissues to make use of the sugar offered them, for, as we have seen, there is experimental evidence that insufficiency of the internal secretion of the pancreas, no matter how it may be caused, results in abnormal glycogenolysis with a consequent increase in the sugar content of the blood. When, therefore, there is an absolute deficiency, such as appears to exist in most, if not all, advanced cases of diabetes it is *probable that the high blood sugar is of dual origin, part arising from overproduction, and part from defective utilization.* That this is the case is indicated by the experiments of Cori and Goltz,[8] who found that a diminished output of sugar by the liver into the blood stream, as well as a larger intake of sugar by the muscles fol-

(7) British Med. Jour., p. 516, 1924.
(8) Jour. Pharm. and Exper. Therap., December, 1923.

lowed insulin injections of animals, showing that the fall in the sugar content of the blood which occurs under these circumstances is dependent on the combined action of insulin on the liver and muscles.

Insulin Shock. That the circulatory insufficiency during insulin hypoglycemia, involved in the so-called "insulin shock" is due to deficiency in dextrose is rendered evident by the studies of D. G. Edwards and I. H. Page[9], who find that intravenous injections of glucose produce a remarkable improvement on such hypodynamic hearts. The depression of cardiac activity is probably due to the lessening of the supply of combustible material in an available form.

C. Bulatao and A. J. Carlson[1] have shown in animals that hypoglycemia produces hunger contractions, that an experimental increase in the level of blood glucose produces inhibition of hunger contractions, and experimental decrease in that level leads either to onset of hunger contractions in the quiescent stomach, or to augmentation of hunger contractions when these are already present.

Lactose, which is not used by the tissues directly, without preliminary digestions, does not exert such an inhibitory effect. In experimental hypoglycemia produced in animals by insulin, increase in gastric tonus and hunger contractions, even of the tetany type, appear as the sugar content of the blood becomes lowered. These phenomena also are inhibited by glucose, but not by injections of lactose. The observations explain the excessive hunger felt by patients as one of the early symptoms of hypoglycemia following large doses of insulin as well as the rapid suppression of hunger in fasting persons on taking sugar by mouth and the depression of hunger, especially in children, on eating candies and other sweets between meals.

(9) Amer. Jour. Physiol., June, 1924.
(1) Ibid.

Orlando H. Petty and Kenneth Knode[2] detail the symptoms of the hypoglycemia reaction as follows:

1. Perspiration in every patient. The skin was cold and clammy and the perspiration was general, the degree varying directly with the depth of the collapse.

2. The patellar reflex was appreciably increased in 50 per cent. of the cases.

3. Pulse and respiration were not markedly affected.

4. Mental depression was more or less present in nearly every case. Two of the patients were unconscious. The authors accounted for one of these cases through failure to have his evening meal consumed at the proper time after the insulin had been administered. The other case was a man that had an infected gangrenous foot amputated three days previously, and, as has been frequently observed in diabetics following the cleaning up of an infection, this patient's tolerance suddenly increased, or his insulin requirement decreased and he went into collapse following his evening insulin and meal. One case, a boy aged thirteen years was loquacious, threw himself about the bed as would a severe case of chorea, and his face was flushed. The remainder of the cases displayed a very typical dulled or clouded mentality. They had a dazed or vacant expression, could not answer questions quickly, were slightly confused as to orientation, drawled their speech like those slightly under the influence of liquor, and had some difficulty in enunciating their words distinctly.

5. Practically every patient complained of feeling weak and very hungry, and of partial loss of coordination of the voluntary musculature.

6. Diplopia in 2 cases, both children.

The blood sugars of their series are:

	mgm.
Highest	0.099
Lowest	0.042
Average	0.071

(2) Amer. Clin. Med., November, 1924.

In diabetics whose blood sugars were high, that is above 300 mgm., symptoms of insulin shock frequently have been observed when their blood sugars were rapidly reduced to within usual normal range. The cause of this hypoglycemic reaction has not been determined. MacLeod believes that the immediate cause of the symptoms is the development of some toxic condition in the nerve cells, the prevention of which in the normal animal is dependent upon a certain percentage of glucose in the tissue juices.

The hypoglycemia can usually be avoided if the dose and time of administration is arranged to suit the individual case, and in those who are emanciated insulin dosage and diet should be so arranged that their urine will be sugar free and blood sugar not below 150 mgm. per 100 c. c., thus giving a larger margin for variations in the intake or absorption of carbohydrate. The author has seen no case of unconsciousness in hypoglycemia which could not quickly be differentiated from diabetic coma and rapidly restored to normal. Should it be impossible to make such a differentiation, procure blood at once for a glucose estimation by veni-puncture and immediately administed 10 grams of glucose. Within 30 minutes the blood sugar estimation should be completed, giving definite data for the administration of either glucose or insulin.

Treatment of Collapse. Only carbohydrates and in a few instances a cup of hot black coffee were used in the treatment of these cases. The carbohydrates were administered in the form of orange juice except in three cases when cane sugar dissolved in a small quantity of water was given. The glucose that was given intravenously was in the form of a 20 per cent. aqueous solution, sterilized by fractional sterilization in an Arnold steam sterilizer. The authors now use ampules of glucose prepared especially for intravenous administration. 40 per cent. of the cases received no carbohydrate. Their symptoms were of such a mild nature that no treatment

other than a cup of hot coffee or absolute rest in bed was necessary to relieve them. The more severe cases require a few grams of carbohydrates by mouth in the form of orange juice, sugar, syrup or candy, while those who are unconscious should be given a hypodermic injection of epinephrin 1 c. c. of 1:1000 solution followed by sugar, syrup or other concentrated carbohydrates by mouth when the ability to swallow is restored by the epinephrin injection. If the epinephrin does not restore the function of deglutition within a few minutes then 15 or 20 grams of glucose should be administered intravenously. This promptly restores the patient.

Every case to whom carbohydrate was administered obtained complete relief in from five to ten minutes. Those cases that received no medication except a cup of coffee and rest were a little slower in recovering but recovered none the less completely.

Insulin in General Practice. George Graham[3] maintains that insulin can be used in general practice with great advantage to the patient and without any danger, provided certain precautions are observed. The ideal of treatment is to maintain the blood-sugar within normal limits if the patient is to continue to progress satisfactorily. Nevertheless, he considers blood-sugar observations not essential provided that the urinary sugar is watched and the effect of the insulin observed. Before starting treatment it is important to discover and treat any sources of infection, such as boils, pyorrhoea, or other septic foci. Tuberculosis of the lungs should be sought for most carefully, as it is a common complication in long-standing cases. It is a good plan to start the treatment with an attempt to get the urine sugar free by dietetic measures. If, on a maintenance diet, the patient continues to pass sugar, 10 units of insulin should be injected before breakfast, and the urine collected in approximately three-hour periods throughout the day. The urine should be tested qualitatively for

(3) Lancet, Jan. 12, 1924.

sugar by Fehling's or Benedict's test. A nurse or the patient can soon learn to do these tests and keep a three-hourly chart of them for the doctor. If the patient is passing sugar, the blood-sugar is over 0.19 per cent., and the urine passed in the first three hours will certainly contain sugar. If, however, the blood-sugar has decreased, there will be no sugar in the urine from three to six hours after the insulin. If, however, the dose of insulin was not big enough, the blood-sugar will not fall below 0.19 per cent., and sugar will be present in every specimen. In this case, after three days, the dose of insulin should be increased to 15 units, and if the specimen of urine still contains sugar, the dose must be increased to 20 units after another three days. If the dose of insulin is sufficient to lower the blood-sugar below 0.19 per cent., the urine from three to six hours will be sugar-free, but that from six to nine hours will contain sugar, if the blood-sugar has risen above 0.19 per cent. If this occurs the dose of insulin should be kept steady, and the urine of the period from six to nine hours tested daily. If the dose of insulin is adequate the sugar-tolerance of the patient will improve, and the urine of the period six to nine hours will become sugar-free. If it does not, then the dose of insulin must be increased. If the urine for six to nine hours becomes sugar-free, the urine from nine to twelve hours must be tested, and this in turn will become sugar-free. This process must be continued until the urine is sugar-free throughout the 24 hours.

At this stage it is a great advantage to know what the blood-sugar is, but if this is not possible it can be gauged by watching the effect of the insulin. An adult who has a normal blood-sugar cannot take more than 10-12 units on this diet without having mild symptoms of overdosage. It is not necessary to give sugar for the mild symptoms like sweating or inertia as a hot drink, an egg, or a tomato will at once relieve the patient. If there be serious symptoms it is well to warn the

patient or nurse that 1 c. c. of adrenalin, 1:1000, subcutaneously will at once relieve the symptoms, or two to four lumps of sugar by mouth.

If no symptoms of overdosage occur after 20 units it is probable that the blood-sugar is above 0.14 per cent., and the insulin should be kept steady at 20 units until symptoms are produced, and should then be decreased by 2 units at a time, watching the patient carefully.

The above procedure is necessary for the patient with severe diabetes, who continues to pass sugar even after severe dietetic restrictions. Most patients cease to pass sugar on diet, but the blood-sugar may still be high, 0.17 per cent., and it is an advantage to know the blood-sugar at this stage. If this is not possible, a dose of 10 units should be given each day, and the effect of increasing the dose to 12 or 14 units watched. If, after 14 units, no symptoms of overdosage such as sweating or a feeling of inertia are observed, the blood-sugar is probably above 0.14 per cent. The dose should be kept at 14 units until symptoms appear, and then decreased to 12 or 10 units.

In the treatment of coma it is usually safe to give 30 units of insulin. But a dose of 50 gm. of dextrose by mouth or by esophageal tube cannot do any harm. If the patient has not shown any sign of returning consciousness in three hours another 20 units should be given. The dosage can be gauged by testing the urine every three hours. If sugar is still present from three to six hours after the injection it is safe to give another 20 units. If there is no sugar in this specimen no insulin should be given until sugar reappears, and then only 10 units. In this way the dose of insulin can be regulated with safety. It is better to give water only for two days, and then start on the gradual ascent of the ladder diet. It is most important to search for signs of infection, as in four out of five cases of coma an acute infection has been found. If this is the case, the caloric

value should be rapidly increased, and the insulin dosage regulated accordingly.

Patients suffering from such conditions as carbuncles, gangrene of the leg, appendicitis, etc., should be prepared for operation by treatment with insulin. If the operation can be delayed for a few days it is better to get the urine sugar free by fasting and insulin, but if the operation is urgent a dose of 30 units of insulin and 50 gm. of dextrose should be given immediately before the operation. Afterwards the diet for some days should consist of the ordinary diet which is given to this type of case,—milk, etc. The sugar output is watched by testing each specimen of urine and giving insulin on the same system as that described in the treatment of coma. The anesthetic should be gas and ôxygen by preference, but if this is not sufficient a little ether may be given as well. Local or spinal anesthetics are very good.

The minor ailments, such as "colds in the head," tonsillitis, etc., require careful treatment. They should always be taken seriously, and the patient should go to bed. It is better to reduce the diet by one-third and add another 5 units to the dose of insulin. When the patient is better the food can be increased again. Whether the infection acts directly on the B cells, or indirectly by causing a demand for a bigger output of insulin than they can produce, is unknown. The minor infections are largely responsible for the decline in sugar tolerance which was so disappointing in the old days. One important point in the treatment is to relieve the constipation which is nearly always present, and especially when the patient is comatose.

Insulin in Diabetes with Infection. I. M. Rabinowitch[4] also noted that the "blood-sugar time curves" obtained following the administration of insulin in the cases of diabetes mellitus complicated by infection presented one phenomenon in common, namely, the absence of the characteristic rapid onset and steep nature of the

(4) Canadian Med. Ass'n. Jour., June, 1924.

fall of the blood-sugar. In isolated instances with septicemia and severe acidosis only the slightest changes were noted in spite of the enormous doses of insulin (100 units) administered.

Fever seemed to be an influencing factor in the great majority of cases. In the absence of fever characteristic curves were obtained. Though in the greatest number of cases the slow response to insulin was associated with fever, such a reaction was noted in the absence of fever, but in the presence of suppuration.

The curves obtained from diabetics, complicated by infection at the time of admission of the patient to the hospital, were no index to prognosis. In 26 such cases including gangrene, carbuncle, abscess, etc., there were only four deaths. Sixteen patients were eventually able to do without insulin, dietary restriction alone sufficing. These patients apparently, prior to the complication, were mild diabetics, the pancreatic function being suddenly deranged by infection.

Hence in the presence of infection no routine course can be followed in establishing the dose of insulin. Enormous doses may be required. The amount and frequency of administration during the emergency period is best determined by the frequent (hourly if necessary) estimation of the blood-sugar.

Dosage of Insulin. Russell M. Wilder[5] insists that, in diabetes, reliance on the oral administration of the pancreatic preparations thus far prepared has so little justification that such practice merits the most vigorous condemnation. To deny insulin to a patient with a tolerance for carbohydrate low enough to require it, and to substitute for this now well established drug some oral pancreatic medication, is comparable to treating operatable cancer by massage. Many of the reputed anti-diabetic pancreatic preparations on the market have been subjected, by C. J. Kemper, to the scrutiny of clinical tests. None of those thus tested have shown

(5) Jour. Amer. Med. Ass'n., Oct. 4, 1924.

any effect on blood-sugar or glycosuria. Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times as large.

On the other hand, purified extracts containing the internal secretion of the pancreas (insulin) and suitable for subcutaneous injection have a prompt and powerful action when so administered. The subcutaneous injection of insulin in diabetes causes the blood-sugar level to be depressed, glycogen to be stored, the oxidation of sugar to be promoted, and acidosis to be checked. Because its action is so powerful, and because a depression of the blood-sugar to a very low level may have fatal consequences, this new product cannot be employed with the reckless abandon that sufficies for the majority of endocrine preparations. The Toronto *insulin unit will promote the metabolism of approximately 2 gm. of glucose* in uncomplicated cases receiving standardized diabetic diets. The physician may therefore gage his insulin dose with great precision. He must know how much glucose the patient will derive from his food and metabolism, and how much insulin the patient himself can provide from his insulin-making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case, insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed, insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

Doses of from 5 to 20 units administered once, twice or three times daily suffice in uncomplicated cases if the diet is properly adjusted. When complications are

present, especially infections, and in the presence of diabetic coma, doses of 15 to 30 units are given at intervals of from three to six hours, accompanied by oral administration of easily available carbohydrate. Orange juice has been found useful for this purpose.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's antidiabetic function. In the severe cases, the evidence now available is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation alone.

Induced Hypoglycemia as a Pancreatic Rest Cure in Diabetes. Helmuth Ulrich[6] believes it possible that diabetic patients who do not show raised carbohydrate tolerence as a result of treatment either have not received sufficiently intensive treatment, or are unable, because of old age or some primary pancreatic or constitutional disease, especially arteriosclerosis, to respond.

The author urges the adoption of *blood rather than urine tests as a guide for the treatment of diabetes.* The fallacy of using glycosuria as a therapeutic control and as a criterion of carbohydrate tolerance is easily shown by the fact that marked hyperglycemia, 300 mg. and possibly more, may be found in some cases of severe diabetes after the urine has become sugar-free. With blood-sugar two or three times the normal amount, the Langerhans tissue of the pancreas, whose function it is to maintain glycemia at its normal level, is of necessity still over burdened, even though glycosuria be absent. It is not surprising, therefore, that treatment guided by urinalyses has effected but little improvement in carbohydrate tolerance. It would seem that a carefully controlled prolonged period of induced hypoglycemia is the only really effective method of resting the pancreas and

(6) Jour. Amer. Med. Ass'n., Dec. 13, 1924.

of allowing it to resume some of its normal function, provided its power of recuperation has not been lost.

The author reports a case of a young man with diabetes mellitus subjected to a prolonged period of hypoglycemia, which tends to strengthen the belief stated, because on a diet containing but 40 gm. of carbohydrate, the use of 30 units of insulin a day was insufficient to render the patient's urine sugar-free. It was only after insulin had been increased to 45 units that glycosuria disappeared and the blood-sugar was markedly reduced. After a period of probably constant hypoglycemia lasting about four months, on the contrary, insulin was no longer required, even with a diet containing 129 gm. of carbohydrate, or about three times the initial amount, to hold the blood-sugar at or near the normal level.

Time of Administration of Insulin. D. Murray Lyon[7] finds that "insulin given subcutaneously to a fasting patient causes a somewhat slow fall in the blood-sugar during the first half hour. This phase is followed by a much more rapid decline for the next hour or hour and a half, but after the second hour the rate of fall again slows and only a slight further diminution in concentration takes place, although the effect persists for a long time. The minimum point is reached somewhere between the third and the sixth hours, and thereafter the blood-sugar value increases once more. A return to the original fasting level would take place were not the diminishing effect of several hours of starvation superadded. The whole reaction caused by 10 units of insulin lasts more than eight hours, and in many cases the effects are still noticeable twelve to sixteen hours after injection."

Observations have been made on the blood-sugar changes and on the urine in patients taking a standard breakfast with a uniform dose of insulin at different intervals before the meal. The results are shown in Fig. 10.

(7) Lancet, July 26, 1924.

On the basis of these observations it has become the author's practice for the past six months to employ an interval of about two hours between each dose of insulin and the meal which follows. By this plan glycosuria is

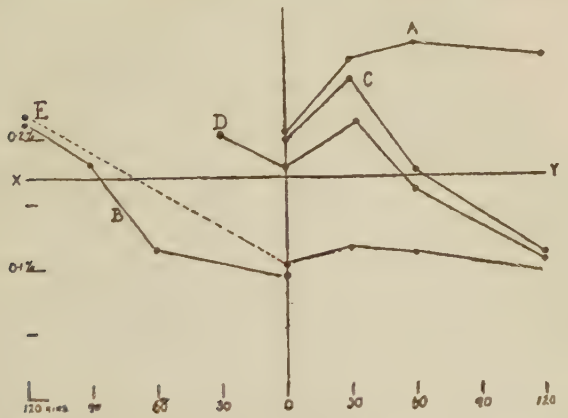


Fig. 10.—A standard breakfast was given at the point 0; the figures on the abscissae indicate minutes before and after commencing the meal. Curve A, blood-sugar changes when no insulin was given. B, Effect of 10 units of insulin on the fasting blood-sugar. C, Breakfast and insulin taken at same time. D, Insulin given half hour before food. E, Insulin two hours before breakfast. X-Y, Normal level of renal threshold.

avoided and the patient is able to make the fullest use of the insulin given. It was thought that although the two-hour interval was the most satisfactory to employ in the morning before breakfast when the fasting blood-sugar required to be brought down to the normal level, a shorter period between dose and meal might be sufficient throughout the day. When the point was investigated, however, it was found that shorter intervals at these times were less satisfactory than the two-hour period. If only half an hour was allowed the dose of insulin had to be increased to produce the same effect. For these reasons it is claimed that the *maximum value of the drug is obtained*—that is, the largest quantity of food can be "covered" by a definite quantity of insulin

—if a period of about two hours elapses before food is taken.

It has occasionally been found in very severe cases of diabetes of long-standing that *on commencing treatment the first doses of insulin given two hours before food are followed by rather severe symptoms* of hypoglycemia, but that a few days later, under apparently the same conditions, no attack occurs. In explanation of this it is suggested that the effect of the insulin does not depend on the height of the blood-sugar alone, but also to some extent on the glycogen content of the tissues. The view has been taken that insulin creates in the tissues a vacuum for glucose. In these severe cases of long standing the tissues contain very little or no glycogen, and under insulin they are able to take in rapidly a very large proportion of the sugar circulating in the blood, so that hypoglycemia is easily induced within two hours. A few days later, when the glycogen content of the tissues has improved, the transference of glucose into them under the same dose of insulin is much less rapid and no symptoms occur in the two-hour period. It would therefore be desirable *in emaciated subjects, when commencing the use of insulin, to allow an interval of only half an hour between the dose and the meal following for the first three days and thereafter to lengthen the interval to two hours.*

The object to be aimed at in employing insulin is to keep the blood-sugar within normal limits, not only during the digesting periods, but throughout the whole 24 hours. Where the total quantity is small (5 or 10 units) it may be given as a single dose, but this method is unsuitable for injections of over 20 units. Then it is usually found most convenient to divide the insulin into two or three portions.

The action of the insulin on the blood-sugar can be followed in two ways, (a) by making frequent estimations of the blood-sugar; (b) by examining each quantity of urine passed. The former method is doubtless

more accurate, but is distasteful to the patient. The second plan has a much wider application, and may even be undertaken by the patient himself. It consists in examining two-hourly specimens of urine from 6 a. m. to 10 p. m. and a collected sample for the hours of sleep. This method readily shows whether each meal is adequately covered. Frequent sampling will show at once where the leak occurs.

When two or three doses of insulin are given during the day-time within a space of about eight hours (say from 8 a. m. to 4 p. m.) the influence of the last dose has disappeared long before morning, so that the blood-sugar values creep up during the night, and glycosuria occurs before breakfast. Early morning glycosuria proved very troublesome in certain cases until steps were taken to control the blood-sugar during the night as well as in the day-time. This was accomplished by separating the first and the last doses of insulin as widely as possible, allowing not more than 12 hours between the evening dose and the morning one. As the return of sugar in the urine is always a disappointment to the patient, it should be avoided if possible. It is a good plan to insist on such a patient taking a lower diet once a week. Instead of his usual 2,500 or 2,800 calorie diet he drops for one day to 1,200 or 1,500 calories, at the same time continuing his insulin as usual.

The lag effect is also seen in the opposite direction. In certain cases, as treatment advances, the patient begins to find that he experiences slight symptoms of hypoglycemia—hunger, slight flushing, perspiration, or shakiness—about 1¼ or 1¾ hours after the insulin has been injected. These symptoms may also appear for the first time after the patient has apparently been stabilised on a definite food insulin balance for several days without having attacks. All patients before leaving hospital should be taught to recognize the signs of hypoglycemia and how to cut short an attack, so no harm results from the appearance of slight manifestations. When this

stage of treatment is reached and the patient is experiencing slight attacks, several courses are open. The interval between the injection and the meal may be shortened. This avoids the appearance of the symptoms and at the same time keeps the blood-sugar at a low level. Alternatively, the amount of food taken may be increased daily until the symptoms cease to appear; or thirdly, the diet may be kept constant while the dose of insulin is reduced. All these procedures have been followed as occasions warranted.

It has not yet been definitely decided whether in all cases an endeavor should be made to keep the fasting blood-sugar level as low as possible, or whether as good results are to be obtained by merely avoiding glycosuria. The former plan would seem to be preferable, at least for a time, during the earlier stages of treatment, but of course it requires larger doses of insulin. The tendency to occasional variability in the strength of the insulin must be kept in mind when an unexpected reappearance of glycosuria occurs.

F. M. Allen,[8] to avoid undue hyperglycemia before or after breakfast, due to the long period without insulin during the night, shortens the long night period by giving the first insulin dose about an hour before breakfast (usually immediately on rising) and the third dose about an hour after supper, or even at bedtime.

Precautions in the Use of Insulin. Arthur R. Elliott[9] emphasizes the following points to be remembered in guarding against hypoglycemia:

1. In the giving of insulin there is probably a natural tendency to the increase of sugar tolerance, which grows unconsciously and without our knowledge. The same unitage of dose which has been nicely balanced against the patient's sugar level on the first of the month may on the last day of the month be excessive because of the natural increase of the pancreatic hormone. In that

(8) Jour. Amer. Med. Ass'n., June 14, 1924.
(9) Surg. Jour., August, 1924.

case the patient may burn up more sugar than is available above the stage of safety, thus giving rise to some degree of hypoglycemia.

2. If the patient be given insulin two or three times a day there may be a summation of effects which will induce an unexpected hypoglycemial reaction.

3. When insulin is administered, the next succeeding meal should be given promptly on time, because sometimes a speedy reaction occurs and if the meal is not given early a hypoglycemial reaction may occur. In the same way, any delay in the ingestion of food or its wastage by vomiting or diarrhea may, by depriving the individual of the expected amount of glucose, give rise to hypoglycemia.

4. Changes in the activities of the individual have much the same effect. A man who expends a large amount of energy will burn up more sugar than would be the case if he were at rest. Therefore a change in the person's habits without a corresponding change in the amount of insulin administered may have a disastrous effect.

5. Then again, after the acids have been burned up and the excess of glucose has been disposed of, large doses of insulin may induce hypoglycemia.

Local Reaction Following Injection of Insulin. To lessen the local reaction to insulin, Banting, Campbell, and Fletcher[2] warn against the intramuscular injection, saying that this adds to the subsequent pain and tenderness and is sometimes followed by induration. They state that tenderness varies with different preparations of insulin, and that at its worst it is confined to slight induration involving the subcutaneous tissue, with reddening of the skin immediately surrounding the point of puncture.

Mills Sturtevant[3] reports the case of a woman who with the first and subsequent injections for about six

(2) Jour. Metabol. Res., November-December, 1922.
(3) Jour. Amer. Med. Ass'n., Mar. 22, 1924.

weeks developed a hard, painful nodule, similar to those felt after injection of typhoid vaccine, lasting about seventy-two hours, and then gradually passing away. This was so severe as to lead to consideration of the advisability of discontinuing the treatment. However, after about forty-five days, the reaction quickly stopped, as if desensitization had been accomplished. The case is reported since it holds out hope that in other, similar, exceptional cases cessation of reaction will come.

Insulin as an Investment. Reginald Fitz and William P. Murphy[4] distinguish between two classes of diabetic patients: those to whom insulin is a necessity and those to whom insulin is a luxury. The group of patients to whom insulin is a necessity is comparatively small and does not represent more than a third of any large series. As a general rule, insulin should be given in all cases of diabetes occurring in children and in people under 40; in all cases of coma or severe acidosis; in all cases complicated by an infectious process which has caused either a temporary or a permanent lowering of tolerance; in all cases of proved severity in which there is necessity for a surgical operation; and in all cases in which the tolerance without insulin, as determined by adequate dietetic control, is so low as to make efficient living impossible. No one should hesitate to urge such patients to take insulin at all costs, for the drug may be life-saving and almost always represents a sound financial investment for the patient with a big dividend of strength and vitality.

Insulin, on the other hand, is a luxury for patients with mild diabetes who are seen most commonly. Insulin offers them but little as a financial investment. If patients of this type wish to take small doses of insulin and can afford it, there may be no reason why they should not, and for a few cents' worth of insulin a day add a certain amount of extra food to their diets. They should not, however, be advised to take the new drug;

(4) Jour. Amer. Med. Ass'n., Feb. 9, 1924.

rather should they be encouraged to get along without it as far as possible, or to use it sparingly.

Insulin Substitutes. Nellis B. Foster[5] tried the effect of "Glycosin," a pancreatic extract suggested by Torrey,[6] on two well studied cases of diabetes. In none of his observations was there any effect noticeable other than would have been expected after insulin was discontinued. Stanly R. Benedict reports that oral administration of the Torrey preparation to a dog was without influence on the concentration of the blood-sugar, even though it received three times the human therapeutic dose of the pancreas preparation in water through a stomach tube.

In the wake of careful scientific studies, there has been naturally a revival of the claims made for various nondescript preparations of pancreas given by mouth. They were tested years ago and found worthless, and the numerous testimonials sent out by their manufacturers are remarkable for the absence of any name connoting knowledge of diabetes or, indeed, of medicine. "Unless one is familiar with diabetes in general, and the peculiar reactions of diabetic patients, there is a considerable probability of being misled by the effects of combined therapeutic experiments. The disease is very often mild, sometimes so mild that trivial readjustments in diet arrest glycosuria. Even patients who have been in diabetic coma, due to some transient upset, may a few months later tolerate a diet that is quite adequate and maintain a normal blood-sugar content. Again, some patients can tolerate only a meager diet for months and then, owing to some change that is obscure, acquire the ability to utilize a slowly augmented diet, and gain in strength and weight until the conditions of disease are entirely changed. For these reasons, therapeutic experiments are reliable only when conducted in cases that have been adequately studied and are known to be severe,

(5) Jour. Amer. Med. Ass'n., Sep. 27, 1924.
(6) Amer. Jour. Electrotherap and Radiol., October, 1923.

and each new therapeutic measure must be preceded by a period of relative equilibrium under the old conditions."

Insulin Treatment of Preoperative and Postoperative Non-Diabetic Acidosis. The specificity of insulin in the acidosis and coma complicating diabetes having been demonstrated, William Thalhimer[7] was the first to propose that the various types of non-diabetic acidosis might be treated with insulin just as successfully, and to demonstrate that in post-operative acidosis treated with insulin the results were more rapid and more certain than with the use of dextrose alone. This opens a large new field for the therapeutic use of insulin, one unforeseen by its original investigators.

David Fisher and Myron W. Snell[8] report two cases of preoperative acidosis which emphatically demonstrate the specificity of the insulin dextrose treatment. By this means a comparatively poor surgical risk may quickly be transformed into a fair or good one. By this means it is not at all necessary to wait for the disappearance or diminution of the acetone and diacetic acid from the urine before proceeding with operation; and, when the time element is an important factor, this procedure can be carried out during the course of the operation; for the action of the dextrose in combination with the insulin is specific and can be depended on. Since dextrose in itself is a diuretic and tends to deplete the body of its fluids, it is good custom to administer fluids by rectum simultaneously with the giving of the insulin and dextrose.

Dextrose alone does not clear up the condition promptly. It may take five or six days to effect this. Only after the addition of insulin are the desired results obtained quickly. To give insulin alone is to assume the presence of a sufficient available quantity of carbohydrate in the body, which usually is not the case in these non-diabetic conditions, and hence renders such a pro-

(7) Jour. Amer. Med. Ass'n., Aug. 4, 1923.
(8) Ibid., Mar. 1, 1924.

cedure dangerous. It is quite important that enough dextrose be administered to take care of the number of units of insulin given, and it is best to give enough so that there will be some dextrose remaining in the blood stream after the insulin has been utilized, furnishing a safety valve on the sugar content. Three grams of dextrose should be given for every unit of U-20 insulin administered.

The technic employed is as follows: a sterile solution of dextrose, preferably of 10 per cent., is allowed to flow into the vein at a very slow rate until 500 to 1,000 c.c. are given. The time of administration should be at least one hour, the longer the better. The amount of insulin used depends entirely upon the amount of dextrose injected. The total amount of insulin to be given should be divided into two equal doses, and one part given five minutes after the beginning of the dextrose administration, the remainder at the end of the administration. So long as sugar appears in the urine, one need not fear an insulin reaction, for this acts as a safety guide and shows that there is more dextrose present in the blood stream than can be taken care of by the introduced insulin.

Dextrose Infusions and Insulin in Shock. David Fisher and Myron Snell[9] have treated successfully ten cases of shock with 500 to 1,000 c. c. of a 10 per cent. solution of dextrose intravenously, and five minutes after the flow commenced 15 units of U-20 insulin subcutaneously. The dextrose injection was regulated so that it took one hour for the complete flow, and at the end of this time, 15 more units of U-20 insulin was given. Within one to two hours following the administration patients begin to react favorably and in some of the cases the result seemed little less than miraculous. The rationale of the treatment evidently is that in shock, as in some other abnormal conditions, we have a state of perverted body metabolism, and that the body cells can-

(9) Jour. Amer. Med. Ass'n., Dec. 13, 1924.

not metabolize introduced carbohydrate as quickly or as satisfactorily as in an individual with normal metabolism. In addition to this, the entire system is in a state of exhaustion, and to overcome it, a source of energy is needed which will readily give up its energy to the dying cells. Dextrose administered alone cannot always do this satisfactorily or quickly enough. As insulin favors the utilization of glucose, the introduction of the insulin causes a rapid oxidation of the introduced glucose, supplying energy so sorely needed. Since time is always an important factor in the treatment of shock, the tremendous advantages of insulin and dextrose over dextrose alone can readily be appreciated. The physiologic background of the action of insulin and dextrose in shock is the same as that in preoperative or postoperative non-diabetic acidoses, or in the toxemic vomiting of pregnancy and eclampsia.

The value of this method of treatment has recently been confirmed by G. Ginsberg[1] who reports a case of hyperglycemia, glycosuria, and acidosis following trauma in which 18 units of U-20 insulin given in the morning, and 200 c. c. of 10 per cent. dextrose intravenously caused immediate cessation of vomiting, negative urine and recovery. Thus, a condition extremely serious and progressing rapidly was immediately transformed to normal convalescence by the use of insulin and dextrose.

The authors emphasize the following points in the technic of administration. For every 3 gm. of injected dextrose, one unit of U-20 insulin should be used. So long as glucose appears in the urine, one need not fear an insulin reaction, for this acts as a safety guide and shows that there is more glucose present in the blood stream than can be taken care of by the introduced insulin. This glucose can be driven off by the injection of a small additional amount of insulin. Since glucose has a diuretic action, and tends to deplete the body tis-

(1) Jour. Amer. Med. Ass'n., May 24, 1924.

sues of fluids, it is a good custom to give at the same time fluids by rectum or hypodermoclysis.

The whole question of insulin in non-diabetic conditions was well summed up in a recent editorial in the Journal of the American Medical Association (May 24, 1924): "there is sufficient background to the project of testing the curative powers of insulin-glucose treatment for pernicious vomiting and other comparable conditions to warrant giving it careful consideration. The procedure is not free from some element of danger that should not be minimized. Insulin therapy demands care in the case of the diabetic patient; doubly great is the need of intelligent precaution with the non-diabetic patient."

Thyroid

Treatment of Myxedema with Thyroxin. Arnold S. Jackson[2] points out that myxedema is easily and frequently overlooked, since the patients make very little complaint with regard to their condition and it is, therefore, necessary to elicit the history by careful questioning. Contrary to the old and generally accepted idea, myxedema does not develop in connection with goiter.

The special senses of sight and hearing are usually disturbed, the hair is sparse, and the skin dry and scaly. The patients are obese, drowsy, lethargic, and suffer with rheumatic pains and a sensation of chilliness. In women the voice undergoes a striking change, becoming coarse and husky. Anemia, slow pulse, subnormal temperature, low systolic blood pressure, polyuria, and mild gastric achylia may be noted. Slow pitting edema, more marked in the legs, is characteristic. Diagnosis may be confirmed by a basal metabolic rate determination of less than —10 per cent., and the progress of the disease may be thus measured.

Improvement following the administration of thyroxin is spectacular and almost immediate. The reaction of

(2) Illinois Med. Jour., December, 1923.

the patient is expressed by headache and general aching. The mentality, facial expression, voice, body temperature, weight, skin and general appearance rapidly return to normal, and edema disappears.

Fifteen milligrams of thyroxin administered intravenously are required to bring the basal metabolic rate of myxedematous patient to within normal limits. A variable daily dose of from 0.8 to 2 mgm. of thyroxin by mouth is required to maintain this level.

Thyroid Dosage. E. Nobel and A. Rosenblüth[3] recommend in children with myxedema the use of 0.01 mgm. per square of the centimeters of the sitting height. For instance, with a sitting height of 60 cm. the dose is 60 times 60, or 3,600 times 0.01 mgm. which is 0.036 gm. of the dried gland.

Parathyroid

Parathyroid Therapy. Macdonald Critchley[4] records the present position of parathyroid therapy as reflected chiefly by his experience as follows:

In the only syndrome definitely known to result from parathyroid upset, the tetany following thyroidectomy, parathyroid medication by mouth is ineffectual. The same is true in other clinical varieties of tetany.

In some 45 cases of the Parkinsonian syndrome, both primary and post-encephalitic in type, the gland seemed to exercise a beneficial control upon the tremor, and also upon the patient's general comfort and sense of well-being. The disagreeable sensations of heat, the salivation and sweating, and the occasional bulbar manifestations are also favorably affected; the rigidity, however, is unaltered. Parathyroid should therefore be administered in combination with hyoscin which has such a definite effect upon the hypertonus. As with other drugs, it is noticeable that the post-encephalitic cases show much less response to treatment than the senile

(3) Wien. Klin. Wochenschr., June 26, 1924.
(4) Practitioner, July, 1924.

cases. In the sixteen cases of chorea in which the author employed the extract, he derived benefit in one case only.

Parathyroid has for some years been a popular remedy for chilblains, but the author has never been able to convince himself of its value in this connection. He has seen crop after crop appear even whilst the patient was still taking the gland. He has treated five cases of purpura by these means without the slightest benefit. Bone disorders have also proved equally intractable to parathyroid medication.

The clinical value of parathyroid therapy in cases of varicose ulceration of the leg seems established. Groves and Vines have published eight cases treated successfully by these means; the author has used it in five patients with decided benefit. Its value in gastric ulceration, pyorrhea, ozena, and rheumatoid arthritis is not conclusive. Six cases of chronic toxic arthritis which he treated with the extract have shown no improvement whatever.

Parathyroid medication does not appear to have the slightest value in the prevention of acute bacterial invasion. However, a series of 43 cases of whooping-cough treated with parathyroid showed a definite improvement in the violence and frequency of the paroxysms compared with the control cases.

Parathyroid treatment in other endocrine disorders has been successful in one type of case alone—namely, Graves' disease. He has treated eleven cases of Graves' disease in this way with distinct improvement in every case; the tremor, nervousness, and tachycardia in particular showed material benefit; whilst in five cases there was also a reduction in the proptosis and in the goiter. Untoward symptoms arising from prolonged or excessive dosage are not common. Grove and Vines have stated that any septic process in the body may suddenly assume an acute phase during parathyroid treatment. Erythema of the face occurred twice in their experience.

Hypophysis

Hypophysis in Diabetes Insipidus. Leonard G. Rowntree[5] reports that consistently good results can be obtained only from the frequent subcutaneous administration of the extract of the posterior lobe of the pituitary. When obstetrical pituitary extract was not sufficiently effective, surgical pituitary extract proved decidedly more satisfactory. However, in a few cases, effects of considerable value were obtained at times from its intranasal use, as a spray, instilled into the nostril by a medicine dropper, or applied on a pledget of cotton. Rectal administration was sometimes helpful, but only for short periods, usually for from two to four hours. Oral administration, in the form of tablets or liquid, was extremely disappointing. In some of the milder cases, the patient felt that there was slight relief at times; but, considering the series as a whole, significant reduction in thirst and urinary output was not effected, despite the fact that tablets coated with phenyl salicylate were employed in some instances.

H. Molitor and E. P. Pick[6] attempted to solve the question why hypophysis in man, especially in cases of diabetes insipidus, always causes a lessening in the quantity of urine, while in ordinary experiments on animals under anesthesia an increase in the secretion of urine was generally observed. They used for this study, dogs with urinary bladder fistulas, that otherwise were in normal condition. These experiments showed, in correspondence with clinical experience, an intense inhibition of water secretion which lasted for from 2 to 10 hours. In contrast to the pressor and oxytocic effects this antidiuretic action is not only observable in the posterior but also in the anterior lobe. Introduction of large quantities of water is insufficient to interrupt this action and leads instead to the picture of "water intoxi-

(5) Jour. Amer. Med. Ass'n., Aug. 9, 1924.
(6) Klin. Wochenschr., Dec. 3, 1923.

cation" shown by weakness, salivation, dyspnea (due to pulmonary edema) and coma.

Analysis of this action shows that it is to a great extent independent of any changes in the kidney and bladder. The vaso-constrictor action of hypophysis, which is very fleeting, cannot explain the urinary inhibition lasting for hours. This is likewise shown by the fact that various vasodilators as the nitrites, or the purins could not reinstate the inhibited diuresis. On the other hand it was easy to antagonize that action by generally acting osmotic agents such as salts, dextrose and especially urea.

These facts demonstrate that the *antidiuretic action of hypophysis is not to be explained by an action upon the kidney but by changes in the extra-renal tissues.* The hypophysis is therefore the most important regulator of water distribution in the system and this action of hypophysis may well be connected with its influence upon growth, as growth without simultaneous change in water distribution in the system is impossible. The favorable influence of hypophysis in diabetes insipidus suggests that this disease is not of renal but of extra-renal origin.

Hypophysis as Stimulant to Involuntary Muscle. Rudolph Klotz[7] considers hypophysis especially indicated in collapse due to dilatation of the splanchnic capillary system, such as occurs in enteritis, peritonitis, and in the depression of the circulation in the course of pneumonia or typhoid fever. In such conditions, he uses 1 c. c. of an active extract intramuscularly. He has also found it useful in chronic asthenia of the involuntary muscles, characterized by low blood pressure, pallor (without anemia) poor pulse, dyspnea on exertion, subjective heart distress and fainting spells, a condition probably due to deficiency in hypophysial secretion, which serves as a stimulating hormone to involuntary musculature.

(7) Deutsche Med. Wochenschr., Aug. 24, 1923.

In paralytic ileus, following laparotomies, the author likewise finds this agent a very useful remedy when given in doses of 4 c. c. intramuscularly, taking at least fifteen minutes for the injection, so as to avoid excessive fluctuations of blood pressure. He has seen copious bowel evacuation occur before the injection had been finished.

Indeed he considers it desirable to employ hypophysis routinely after laparatomies as a prophylactic against the above described conditions, giving 1 c. c. intramuscularly twice a day.

In emergencies, he does not hesitate to administer intravenously 4 c. c. of the preparation he uses (Hypophon-Gene) in ¾ liters normosal solution.

Klotz also finds hypophysis useful in urinary retention and in bleeding of the non-gravid uterus.

Epinephrin

Epinephrin Active on Oral Administration. The generally prevalent opinion that epinephrin is inactive when given by mouth is contradicted by the experiments of B. Aschner and H. Pisk[8]. *Providing sufficiently large doses are administered, there is a definite rise of blood pressure.* On administering, in the morning, on an empty stomach, 3 to 4 c. c. of a 1 pro mille epinephrin solution diluted with an equal amount of water, they observed, usually within five to ten minutes, sometimes not until fifteen or twenty minutes, a rise in blood pressure averaging 30 mm. Hg. with a fall setting in after twenty to thirty-five minutes. Cases with weak or completely absent reaction were also noted. The reaction was not influenced by the HCl of the stomach, which is as may be expected, as epinephrin is not destroyed by Pepsin-HCl in vitro. The degree of reaction in any one case was parallel on oral, subcutaneous or intravenous administration. In other words, the re-

(8) Klin. Wochenschr., July 8, 1924.

activity of the vegetative nervous system is of importance in the reaction rather than a difference in absorption. A change in pulse rate or glucosuria was never noticed in these experiments. Hence the authors believe that for testing of the function of the vegetative nervous system, the subcutaneous administration must still be preferred. The authors are not in favor of intravenous administration in this test as the changes are too rapid and fleeting unless relatively enormous doses are employed.

Absorption of Epinephrin on Hypodermic Administration. The impression seems to be widely prevalent that epinephrin, given subcutaneously, causes little general effect, and that its action is quite uncertain. This view is probably based on the blanching of the skin which is seen around the site of injection, and on the fact that epinephrin causes vasoconstriction of some vessels [as well as the lack of pressor effect when the agent is given subcutaneously to anesthetized experimental animals—Ed.] However, the spectacular relief from distressing symptoms that occurs in asthmatics within a few minutes after a hypodermic injection of a minute dose of adrenalin is, in itself, evidence that absorption by this route is rapid and satisfactory.

When adrenalin is administered hypodermically there develops in the neighborhood af the needle puncture a white zone which increases in size and persists for a long time. In many cases irregular white lines can be traced for some distance centrally from this area. These lines do not correspond to blood vessels but resemble in distribution the red streaks of inflamed lymphatics which appear in cases of cellulitis. This suggests that absorption of adrenalin can take place freely by lymphatic channels.

D. Murray Lyon[9] investigated the response to hypodermic injection of adrenalin in about 50 patients. Records of the pulse rate, systolic and diastolic blood

(9) Jour. of Exper. Med., Dec. 1, 1923.

pressure readings, and the basal metabolic rate were first made with the usual precautions. The subject was then given in the forearm a subcutaneous injection of 0.5 c.c. of adrenalin chlorid 1:1,000 solution (Parke, Davis and Company). Following this, observations were made every 2 minutes for an hour on the blood pressure, the pulse, and respiration rates, and 10 minute samples of expired air were collected over the same period.

In the majority of cases the rise of the blood pressure commenced within 2 minutes after the hypodermic injection, but occasionally the increase was not evident for several minutes. In one instance a latent period of 10 minutes elapsed. The increase of pressure may occur quickly or slowly so that the highest point is often reached in six to ten minutes, or may be delayed for nearly 40 minutes.

The author concludes that adrenalin solution given subcutaneously is usually rapidly absorbed, probably by lymphatic channels. When absorption takes place rapidly a large quantity of the drug comes into action at once, the maximum occurs early, the curve of blood pressure reaches a considerable height, and subsides quickly. When absorption is slow the apex appears later and does not reach so high a level.

Epinephrin Prevents Absorption of Injurious Substances from Abraded Surfaces. Beverly Douglas[1] studied the pressor action of epinephrin, its exact duration and force of action on the most superficial vessels by the following experimental method: the ear of the animal used is abraded by lateral movement of a sharp safety-razor blade held at right angles to the skin surface. Thus, the latter is denuded of epithelium over a measured area previously outlined with ink. So superficial is this abrasion that no bleeding is occasioned. The surface within the outline is moist and red. The pressor drug is then applied for a measured period of time, is

(1) Jour. Amer. Med. Ass'n., Dec. 8, 1923 and Feb. 2, 1924.

washed off with salt sclution, and a symptom-producing substance, such as strychnin, applied in its place.

In this manner he finds that epinephrin chlorid in concentrations up to 1:10,000 produces a peripheral vascular block so complete as to prevent absorption of a toxic dose of strychnin sulphate in saturated solution. In similarly prepared control animals, enough strychnin was absorbed in identical periods of time to produce convulsions in every animal and death in a majority. A single application of the vasoconstricting drug for three minutes was shown to prevent absorption of strychnin for 32 minutes. After intermittent applications of epinephrin for two hours and ten minutes, it is active in preventing the absorption of strychnin. Procain exerts a synergy with epinephrin in preventing absorption, though in the concentrations used its effect is slight. Amyl nitrite relaxes epinephrin constriction and allows strychnin to be absorbed subsequently.

The author outlines the practical results that might be realized from developing a treatment based on these observations as follows: superficial burns quickly exposing large areas to the action of an injurious substance perhaps constitute the most urgent indication for local vascular constriction. But traumatized tissues, infected wounds, erysipelas, pleural empyema and cystitis also offer a broad field for its employment.

In treating such conditions in the future, the author believes that more emphasis should be placed on the early production of a nonreceptive, nonexchanging surface, with vessels, by means of suitable drug action, forced to supply only the normal needs of the tissues instead of being allowed, as usual, to respond to the abnormal demands of organisms that may or may not be overcome in the inflammatory reactions which follow. No organisms can live and multiply unless a suitable medium is provided. Their growth will not be favored by surface conditions such as the ones described. The tissues will not suffer injury from the production of

such conditions, provided details of technic are followed carefully. The author is convinced that the major constitutional symptoms of burns, including the ones causing death after the early traumatic shock period and before the period af infection, are due to material absorbed from the surface. Extremely early intervention by local vascular blocking before or during the early stages of inflammation is always desirable, and in extensive burns is indispensable from the standpoint of the patient's life. It is just as important to prevent a patient from being fatally poisoned through a large capillary bed as it is to prevent his bleeding to death by the application of a tourniquet.

Epinephrin in Post-Scarlatinal Hyperthermia. Heinrich Finkelstein[2] calls attention to the fact that a considerable number of scarlet fever convalescents showed temperature elevations beginning in the third or fourth week after the scarlet fever itself had subsided, and persisting for many weeks. As no infection could be found in spite of the most careful examination, the author considered it a nervous disturbance of temperature regulation and attempted to solve the question by pharmacologic methods, testing patients with those remedies used for testing the autonomic nervous system, namely, atropin, pilocarpin and epinephrin. The dose of the drugs was that indicated by Friedberg as the smallest quantity just effective in normal children—from 2 to 5 decimilligrams (0.2 to 0.5 mgm.) of atropin; from 4 to 7 decimilligrams (0.4 to 0.7 mgm.) of epinephrin, and from 1 to 5 mgm. of pilocarpin, depending on the age of the child.

According to recent investigations, atropin produces fever quite frequently in normal children, presumably by inhibiting perspiration due to diminution of vagus tonus. Epinephrin, also, is known to produce fever, which can probably be explained by heat stases due to contraction of the capillaries of the skin. Pilocarpin

(2) Jour. Amer. Med. Ass'n., Aug. 23, 1924.

either has no effect on the temperature or lowers it somewhat, probably because of increased sweat formation.

The reaction of the subfebrile scarlet fever convalescents was in marked contrast to this reaction of normal children. Atropin was persistently without effect. Pilocarpin always produced high fever, frequently 39 C. (102 F.), whereas the temperature in all cases became normal or even subnormal, following the administration of epinephrin. This effect of epinephrin usually persisted for from two to three days, and, in some cases, the temperature remained permanently normal after a single injection of epinephrin. Control patients with slight infectious temperature elevation were never influenced.

Under these conditions, it seems permissible to attribute this habitual hyperthermia of scarlet fever convalescents to a balance disturbance in the autonomic nervous system or in the heat regulating center. Inasmuch as epinephrin is usually regarded as a stimulant of the sympathic, pilocarpin as a stimulant of the vagus, and atropin as an inhibitor of vagus tonus, if we see in these cases that sympathicus stimulation removes the fever, while vagus stimulation increases the fever, and vagus inhibition has no effect, we are led to think of a relative vagotonia due to weakness of the sympathetic nervous system.

The experience that, in a few cases, a single injection of epinephrin removed the hyperthermia allows us to hope that an effective method of treatment will be found. This is desirable, for, although the hyperthermia is attended with no dangers and does not disturb the general condition of the patient, the members of the family are usually much alarmed.

Epinephrin in Pernicious Vomiting in Pregnancy. Stanley E. Denyer[3] claims that, in cases of vomiting of pregnancy and many other kinds of emesis, it will be found that treatment by administration by mouth of

(3) British Med. Jour., Sep. 13, 1924.

solution of epinephrin in doses of 10 minims of 1:1,000 solution added to 2 drachms of water at three to six hourly intervals, will in many cases be sufficient to stop the vomiting. The diet at the same time should be light and given at short intervals. Those which do not respond to treatment by epinephrin alone should have the following treatment:

1. Rest in bed.
2. Gastric lavage, with solution of sodium bicarbonate, 1 drachm to the pint, one or two pints being used.
3. Solution of epinephrin, 5 minims hypodermically every three hours for a few doses until the vomiting ceases; or the epinephrin solution may be given by mouth in doses of 10 to 20 minims in a little water.
4. The omission of all feeding by mouth, at first, and feeding by rectal salines containing from half an ounce upwards of glucose to the pint, with a small quantity of sodium bicarbonate added if there is any diacetic acid in the urine.
5. The addition to the evening salines of 30 grains of potassium bromid to help sleep and reduce irritability of the nervous system.
6. The gradual increase in feeding by mouth, beginning with small feeds of water as described above.

[This treatment without epinephrin usually checks vomiting—Ed.]

How to Avoid Epinephrin Intoxication. In view of the fact that epinephrin is so often given with local anesthetic, H. E. Symes-Thompson[4] believes it is time to consider its toxic effects more generally than has been done heretofore. Even ½ a minim of a 1:1,000 solution of epinephrin chlorid, at a strength of 1 part in 40,000 has produced disagreeable symptoms. A woman of 28, with slight symptoms of Graves' disease and a goiter of considerable size, died after injection of 65 c. c. of a ½ per cent. procain solution, and a little more than 2 c. c. of 1:1,000 adrenalin chlorid with symptoms so similar

(4) Lancet, Apr. 12, 1924.

to those of a positive reaction to Goetsch's test as to incriminate the epinephrin rather than the procain.

Goetsch's test, used to differentiate hyperthyroidism from certain functional nervous disorders and from early tuberculosis, consists of injecting subcutaneously 0.5 c. c. of a 1:1,000 solution of adrenalin chlorid. A positive result consists in a rise of at least ten points in both blood pressure and pulse-rate during the first quarter of an hour, together with heart consciousness, asthenia, a feeling of dread, tremor, pallor, and flushing, and some sweating. Whatever the theoretical basis may be, there is little doubt that adrenalin produces the results claimed in cases of hyperthyroidism. As in cases of hyperthyroidism, tremor and nervousness are produced or increased and the pulse may become irregular, unequal, and varied in volume, probably few physicians would agree to their patients being subjected to the test if they were aware that it is liable to produce such results as these, unless the diagnosis was impossible by other means. As there are other methods of differentiating between hyperthyroidism and early tuberculosis the test may be regarded as a luxury.

The author concludes that toxic manifestations from adrenalin might be eliminated in dental practice if dentists were to avoid stronger solutions of this drug than 1:100,000; and that surgeons might escape such manifestations by giving a preliminary injection of a smaller dose of adrenalin than that which it is proposed to employ at the operation; and, in the event of an idiosyncrasy to adrenalin being found to be present, by employing a general anesthetic. It is probably preferable to use synthetic adrenalin rather than the natural product, as it is claimed to be one-half as toxic. The use of adrenalin in contraindicated when operating on patients with Graves' disease. The practicability of using large quantities of a dilute solution of procain may render it possible to discontinue the use of adrenalin with this local anesthetic.

Epinephrin in Herpes Zoster. W. W. Duke* finds that, in herpes zoster, pain which is difficult to alleviate with anything milder then morphin can be temporarily relieved in a majority of cases by epinephrin. To obtain this effect the dose should be pushed until the patient experiences relief or an epinephrin tremor. The amount necessary to give relief or tremor varies in different individuals from 1 minim up to several cubic centimeters—in fact, it varies in the same individual at different times almost to this extent. As a general rule, it should be given subcutaneously in doses of about 0.5 c. c. at five minute intervals, until the patient is either relieved or shows a distinct tremor. When the tremor appears, the pain in the majority of cases disappears. It usually returns in from two to 24 hours. The dose of epinephrin can then be repeated and continued indefinitely without injury to the patient. As a rule, it makes the use of morphin unnecessary, or at least reduces its necessity to an occasional dose.

SPECIFIC ANTIGENS AND ANTIBODIES

In General

Principles Underlying the Use of Immune Sera. H. B. Cushing[5] discusses the underlying principles and limitations taught us by our 30 years of experience with the use of these sera. In the first place, we have come to recognize the need of an overwhelming dosage to obtain results. Thus, with diphtheria antitoxin, in an average case of a child one gives at least 5,000 units, *i. e.*, enough to neutralize sufficient toxin to kill 100 children. This is apparently true because of the difficulty of bringing the toxin and antitoxin together in the body, and emphasizes the necessity for maximum doses in such fatal diseases as tetanus and meningitis. This rule does

(*) Jour. Amer. Med. Ass'n., Dec. 13, 1924.
(5) Canadian Med. Ass'n. Jour., June, 1924.

not hold true where the serum is used for prophylaxis. For this purpose a small dose is apparently quite sufficient, *e. g.*, 500 units renders a child immune to diphtheria, and in the recent war small doses of antitetanic serum were found effectual in preventing the disease.

A second principle arising from the first is the necessity of producing a concentrated serum. This aim has been achieved in recent years by heating the serum and precipitating it by ammonium sulphate, producing the so-called serum globulins which are concentrated at least six times. Thus we can understand how the method of using the serum of convalescents for treatment, as has recently been done in scarlet fever and poliomyelitis, must be a most uncertain measure.

A third point is the time required by an antitoxin to produce its full effect. In diphtheria the subcutaneous method requires three whole days to reach the maximum concentration of antitoxin in the blood, and the intramuscular method two days. Hence the advisability of giving one maximum dose in the beginning and not repeated small doses. Recently other methods of administration have been introduced to overcome this difficulty. The intraperitoneal method is useful, especially in infants. It is apparently easy and safe, producing no peritoneal irritation and securing a very rapid absorption. However, for efficiency, no method compares to the intravenous, which produces greater concentration in the blood than all others and produces it practically instantaneously. The intravenous method is especially applicable in tetanus and in meningitis. In the latter disease recent investigations have shown it always to be septicemia in the beginning and if the case is seen early, the intravenous injection should always supplement the intraspinous. In fact, the intravenous method should supplant all others, if it were not for the mechanical difficulties of using it, especially in young children; and for the risk of alarming chills and other foreign protein reactions which are apt to occur immediately after its

use. However, the intramuscular route should always replace the subcutaneous.

The fourth principle to which the author refers is the impossibility of overtaking or counteracting toxins which are already fixed in the tissues, *e. g.*, in a severe case of diphtheria with extensive membrane, seen on or after the third day of the disease, no dose of serum or method of administration is going to prevent the later effects on the heart, kidneys, or nervous system. The same principle is seen in tetanus where serum given after the onset of clinical symptoms rarely saves the patient. This emphasizes the necessity of getting the antibodies circulating in the blood at the earliest possible date.

The fifth point is the very rapid elimination of antibodies from the system if they are artificially introduced, *i. e.*, in passive immunity. This is well illustrated in diphtheria by means of the Schick reaction: a positive reaction is changed to a negative one by an immunizing dose of antitoxin but becomes positive again in a few weeks.

A sixth point is the failure of serum through the fact that most microbes have a series of diverse strains, and a serum prepared from one strain may be impotent against other strains. The most familiar instance of this is in the case of the pneumococcus where a serum prepared from type 1 is only efficacious against this type. The same principle was illustrated in the case of meningitis during the late war. When meningitis broke out among the Canadian forces the serum at first used was quite ineffective and it was only on preparing polyvalent serum from many strains that any satisfactory results were obtained. It is often more satisfactory in this disease to use serum from different sources when repeating the dose unless there is definite evidence that the serum first used was effective.

In view of the serious nature of the disease treated it seems we might disregard the remote danger of sudden protein shock and the discomfort of the serum sickness.

The only cases where they have to be really considered are in adults, and especially those giving a history of asthma or other protein hypersensitiveness. The reaction is much less frequent since the new concentrated antitoxin has been in use. Hypodermic injection of epinephrin is the only measure which seems to afford any relief.

A final point is that all serums and antitoxins gradually lose potency on standing. This deterioration is less rapid if they are kept in a cold place and in the dark; but one has only to visit two or three of the larger drug stores at random and ask for some serum to see how these precautions are neglected; and the author thinks it is not too much to say that most of the serums purchased indiscriminately at drug stores are practically inert. It seems unfortunate that there is no system for on official inspection of the product as usually supplied.

Tissue Immunity. S. Nukada[6] finds, by means of experiments upon the isolated rabbit's heart perfused with Locke's solution, that the resistance of the heart of a rabbit immunized by typhoid vaccine was greater than that of the heart of a rabbit not so immunized. This was also the case in the heart of rabbits immunized by bacilli other than typhoid bacilli, such as *bacilli paratyph; A* and *B, B. coli, B. pneumoniae, B. influenzae, B. pertussis,* and *B. pestis.* Hence acquired immunity, at least in typhoid, instead of being principally due to the presence of antibodies in the blood, is caused by tissue immunity; that is to say, by the increase of resisting power acquired by the tissue cells against toxins.

Many facts related to immunity which have thus far been difficult to explain, can now be made intelligible through the theory of tissue immunity. For instance, the case of a typhoid patient who has previously been injected with typhoid vaccine is generally light. This is difficult to explain through the theory of antibodies, but

(6) Japan Med. World, Apr. 15, 1924.

when tissue immunity is taken into consideration, it becomes easy to explain, for we can more readily visualize persistence of immune bodies in the cells rather than in the fluids of the organism. [It may also explain why, in most instances of infection, passive immunization has thus far been a failure.—Ed.]

Vaccination

Intradermal Vaccination. Though the intracutaneous method will probably not displace the simpler cutaneous inoculation in the masses, D. E. Berney[7] believes that where one fears inoculation injuries, as in skin diseases, and where the occurrence of scars is to be avoided, as well as where general systemic reaction is feared, this is an ideal method. Intracutaneous vaccination in human beings was introduced by Karl Leiner, who showed that there follows from this process, (1) an immunity against cowpox virus, and (2) a typical vaccine reaction different from that of the cutaneous method. In this technic of inoculation he used 1 part of vaccine diluted with 100 parts of normal saline solution and sterile water. The amount used for injection was 1/10 of a c. c.; and to avoid the adherence of lymph to the skin when the injection is made, the needle with which the injection is done must not come in contact with the vaccine. The needle must be introduced 1½ cm. (the author found 1 cm. usually sufficient) into the skin and the point must so lie that during the injection the typical intracutaneous bleb arises. At first, two injections in the upper arm were made, but later he made only a single injection. Practically, it is not necessary to be overexact in the dilution of the lymph. Some of the author's own injections were done with a dilution of as high as 1 to 120 and as low as 1 to 70.

Proceed as follows: use a syringe of 1 to 2 c. c. capacity. Boil two needles, a large one and a fine one.

(7) Atlantic Med. Jour., August, 1924.

With the larger needle, the lymph, which is previously diluted, is drawn into the syringe. Then remove the large needle and put on the fine needle, being careful not to force the fluid to the tip of the needle, and inject. After withdrawing the needle the injection point is cleansed with alcohol and iodin.

In the process of intracutaneous vaccination we see two reactions: the primary, which reaches its high point 24 to 48 hours after injection, and the secondary, which occurs ten to fourteen days after the injection, or after the almost complete disappearance of the symptoms of the first reaction. There is no fever or systemic reaction. The intracutaneous method avoids the well-known and rightly feared cutaneous injuries (infection from eczema and other skin diseases; transference to the eye, genitalia, etc.; secondary infections—tetanus, etc.) and also the disfiguring scar. No dressing is required, as there is no external wound.

Diphtheria Antiserum and Antigen

Diphtheria Antitoxin Should Be Given Intramuscularly or Intravenously. Donald MacIntyre and D. W. McKay[8] call attention to the slow rate of absorption of the antitoxin from the subcutaneous tissues. Experiments have shown that *nearly three days elapse before the maximum concentration of antitoxin is obtained in the blood after a subcutaneous injection,* also the total quantity present is only one-third of that obtained immediately by an intravenous injection. It can be seen, therefore, that this constitutes a very important disadvantage, especially in a severe late case of diphtheria. Subcutaneous injection should no longer be employed for routine work, and is now only used very occasionally in giving a desensitizing dose to a patient who has had serum before.

Intramuscular injection should completely displace subcutaneous injections for routine work. Experiments

(8) Lancet, June 21, 1924.

have shown that absorption is about three times as rapid and the difference is very noticeable in the first ten hours, which is often a critical period for the patient. The site chosen for the injection is the outer region of the thigh. There is no danger of injuring any important structures in this area, and a dose of 12,000 units can be given quite easily. This method should be used for all mild and moderate cases of diphtheria.

Intravenous injections should be given only to toxic cases, mostly of the naso-pharyngeal type, with extensive membrane on the fauces, enlargement of the cervical glands, and discharge from the nose; also in laryngeal cases. The results have been encouraging. In most cases only the first dose was given intravenously, and was followed by intramuscular injections. The intravenous dose varied from 6,000 to 40,000 units, the average being 18,000 units. The largest amount given at a single injection was 24,000 units. In the majority of cases, a definite reaction set in about 40 minutes after the injection. Its onset was usually sudden, with chilliness, which soon developed into a rigor. Pyrexia was a marked feature; the temperature often rose to 104° or 105°, and in a few cases it reached 106°. The pulse was often small and rapid and the respirations quickened. In a few instances the patient was slightly cyanosed at the height of the rigor. Vomiting occurred on some occasions, and in one case a profuse urticarial rash appeared during the reaction and remained for half an hour. No reaction occurred in 24 cases. The severity of the reaction did not appear to bear any relation to the amount of serum injected. On the other hand, there seemed to be a distinct connection between the sharpness of the reaction and the severity of the case. Very toxic cases often had no reaction at all, or it was only slight. This feature has been so pronounced that the authors have been

led to regard a definite reaction as a favorable sign, indicating a good resistance on the part of the patient.

Although the reaction was severe in some cases, the symptoms could not be described as very alarming. One case has come under observation where death occurred six hours after the intravenous injection. The authors could only ascribe the fatal issue to the status lymphaticus found post mortem.

Their experience during the past two years has convinced the authors that the *intravenous injection of antitoxin is of great value in severe cases of diphtheria.* The toxic symptoms subside much more rapidly than after an intramuscular or subcutaneous injection. The onset of paralysis also appears to be diminished. On the other hand, *they do not advocate giving antitoxin intravenously to mild and moderate cases where intramuscular injections have proved sufficient.* As the reaction which usually follows an intravenous injection is sometimes very severe, it seems unnecessary to expose moderate cases to the discomfort and even risk of such a reaction.

Diphtheria Antitoxin Intravenously. H. Osgood[9] believes that lives have been saved in a series of 54 patients with very severe laryngeal and nasofaucial diphtheria given intravenous injections of antitoxin in addition to intramuscular injections.

The author formulates the indications for an intravenous injection as follows:

1. Late cases (the patient being ill four days or more without antitoxin), whether moderate or severe in type.
2. Severe and malignant cases, whether discovered early or late in the disease.
3. Laryngeal cases secondary to faucial involvement.
4. "Bull neck" cases, and those with hemorrhage.
5. Cases that do not respond to an ample intramuscular dose.

Contraindications are:

(9) Jour. Amer. Med. Ass'n., Oct. 27, 1923.

1. Cardiac decompensation or severe organic lesion of the heart or blood vessels.
2. Chronic nephritis.
3. Horse serum or protein sensitivity, unless the patient can be successfully desensitized.

The following precautions should be observed:

1. Use only a clear, amber or colorless serum with high titer (1,200 units per c. c. or over). The importance of this must be emphasized.
2. Inject very slowly, at body temperature.
3. Stop the injection if untoward symptoms appear.
4. Keep the patient warm, quiet, and under close observation afterward.
5. Determine protein sensitivity.
   a. If the patient has had no previous serum injections, caution—a preliminary intramuscular dose should be given.
   b. If the patient has had any serum injections in the past (six days or over), caution—an intradermal test should be performed and the patient desensitized.
   c. If the patient has had antitoxin within from four to six days, safe. Skin tests or preliminary intramuscular doses are not necessary before the intravenous injection.

The size of the intravenous dose in the 54 cases ranged from 800 units to 15,000 units in a single injection, and up to 24,000 units when divided into two injections. Patients early in the series received smaller doses than later on. The intramuscular dose ranged from 24,000 units to 72,000 units.

Some patients (50 per cent.) suffered a severe chill with a sharp rise of temperature and pulse. It is conceivable that in moribund or desperately ill patients this might put a dangerous strain on the cardiovascular system. While recognizing the fact that further work must be done and more experience acquired before we can attain full control over the effects of antitoxin

administered intravenously, the author believes that, in weighing the patient's chances for life, the advantages to be derived from the immediate availability of ample antitoxin provided by this method are greater than the dangers.

Until further experience teaches us to estimate more accurately the intravenous dosage, it would appear that a combination of this route with the intramuscular offers certain advantages. An intramuscular dose given shortly before the intravenous dose will be absorbed slowly and will provide a supply of antitoxin which will still be entering the circulation when that from the intravenous dose is falling off. It will also prevent any anaphylactic effects from the latter.

Intraperitoneal Administration. It has been shown by Lesné, Marquézy and Vagliano[1] that on intraperitoneal administration, antitoxin passes into the blood after 45 minutes; on intramuscular in 50 minutes; and on subcutaneous injection in 80 minutes.

New Toxin-Antitoxin Mixture (1/10 L+). Abraham Zingher[2] observed that mixtures with the larger number of L+ doses were not more efficient than those with the smaller number of L+ doses as long as the mixtures were equally toxic (under-neutralized). In fact, mixtures with the smaller number of L+ doses per c. c., but showing greater toxicity for the guinea-pig, gave better immunity results than those with the larger number which were more neutralized. The new mixture of toxin-antitoxin advocated containing 1/10 L+ per c.c. gives excellent immunity results if it is underneutralized and prepared so as to correspond in its toxicity to a given standard.

Toxicity of Diphtheria Toxin-Antitoxin Increased by Freezing. The Journal of the American Medical Association[3] calls attention to the fact that diphtheria toxin-antitoxin when frozen and subsequently thawed

(1) Arch. de. Méd. des Enfants, August, 1924.
(2) New York State Jour of Med., Feb. 1, 1924.
(3) Jour. Amer. Med. Ass'n., Feb. 16, 1924.

before injection may cause severe local and constitutional reactions. Freezing disassociates the combination, and a lesser dosage of toxin may be efficient. It is recommended that, if freezing has occurred, a mixture containing the minimum practical amount of toxin (1/10 L+ dose in an injection) be used.

Scarlatina Antigen and Antiserum

Scarlatina Antigen and Antibody. George F. Dick and Gladys Henry Dick[4], having succeeded in producing experimentally typical cases of scarlet fever by swabbing on the tonsils and pharynx a pure culture of a hemolytic streptococcus isolated from scarlet fever patients (1923), and having found that the hemolytic streptococcus is not usually present in the blood, demonstrated that the streptococcus produces a soluble toxin which is absorbed into the blood and causes the nausea and vomiting, and the rash. They next found that the filtrate of this culture, when used in the proper dilution, gave positive skin tests in 41.6 per cent. of the persons tested who gave no history of scarlet fever, and that it gave negative, or only slightly positive skin tests in all the convalescent scarlet fever patients tested. The action of the toxin is inhibited by convalescent scarlet fever serum, mixed with the toxin or injected intramuscularly before the skin test is made. The skin test was found positive before the attack and negative during convalescence.

When small amounts of this toxin are injected into susceptible persons, they may develop general malaise, nausea, vomiting, fever, and a scarlatinal rash. These symptoms appear within a few hours after the injection and disappear within forty-eight hours. Following this reaction, the skin test is negative, or only slightly positive. By beginning with a smaller dose of toxin, it is possible to immunize susceptible persons without this severe reaction. The toxin is first

(4) Jour. Amer. Med. Ass'n., July 12, 1924.

carefully standardized on human beings in order to determine the skin test dose. Adults are immunized by three injections of toxin at five day intervals, beginning with a first dose equivalent to 300 skin test doses, and increasing to 1,000 skin test doses. Experience has shown that the immunization must be carried to the point of a negative skin test.

The prevention of scarlet fever after exposure is more complicated. In case of definite exposure, skin tests are made as soon as possible. At the same time, a culture of the throat is made on blood agar plates. If the skin test is negative, nothing more is done. In those with positive skin tests, the next step depends on the throat culture. If the plates show no hemolytic streptococci, active immunization is carried out with three doses of toxin. If the throat culture shows hemolyptic streptococci, passive immunization is accomplished by injection of convalescent scarlet fever serum. Thus treated, none of 125 susceptible persons exposed to scarlet fever developed the disease. Two nurses and five others of a control series contracted scarlet fever.

Horses injected with gradually increasing doses of the sterile scarlet fever toxin produce an antitoxin capable of neutralizing a considerable amount of toxin. Its therapeutic value can be determined only by the results obtained from its employment in a large series of cases. When convalescent scarlet fever serum is not available for prophylactic immunization, this concentrated scarlet fever antitoxin may be used.

Dochez's Antiscarlatinal Serum. Francis G. Blake[5] reports a total of 26 cases, with prompt cure in all but one. Not only has the serum been effective in early uncomplicated cases treated on or before the fourth day of the disease, but also in cases with septic complications. In 21 of the 26 cases a single intramuscular injection of 35 to 90 c.c. of serum sufficed to bring about a prompt

(5) Boston Med. and Surg. Jour., July 10, 1924.

recovery within twelve to 24 hours. Nine were moderately severe and had septic complications. In only three of these was more than 50 c.c. used. Of the remaining five cases, one of which was extremely toxic, and four of which were very toxic, two received two injections of 50 c.c. each; one received three injections totalling 185 c.c.; one received four injections totalling 195 c.c., all with prompt recovery; and one, an extremely toxic and septic case with ulcerative tonsillitis, bull neck, thrombophlebitis, and strèptococcus septicemia, received a single injection of 40 c.c. on the fifth day of the disease without benefit.

The author concludes that Dochez's antiscarlatinal serum is a valuable therapeutic agent in the treatment of scarlet fever. The observations which warrant this conclusion are as follows:

1. Intracutaneous injection of the serum in patients with scarlet fever produces a local blanching of the rash at the site of the injection.

2. Intramuscular injection of the serum in therapeutic doses early in the disease is followed by rapid clinical cure as evidenced by critical fall of temperature and pulse to normal, rapid fading of the exanthem, and prompt return to a state of well being.

Measles Antiserum

Convalescents' Serum in the Prophylaxis of Measles. George H. Weaver and T. T. Crooks,[6] in view of the fact that nearly all deaths from measles (90.6 per cent.) were in children under five years of age, conclude that some method of protection against measles is needed, especially for children under five years of age; excepting for babies during the first few months of life, who do not readily contract measles. The use of serum taken from patients convalescent from measles gives promise of such protection.

(6) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

At the Durand Hospital during the spring and summer of 1923, measles convalescent serum was collected for trial as a prophylactic measure. Exposed children who had not had measles were given serum in the wards of Durand and other hospitals, as well as in a few private cases. In all, 63 children exposed to measles were observed. Nine children not given serum, all of whom developed measles, serve as positive controls. Of the four who developed measles after serum, three were given the serum too late. It appears that *the serum must be given during the first week after exposure to be effective.* In only one of 45 cases in which the serum was given at the proper time did it fail to protect.

The method of collection and administration is essentially that of Dogkwitz (1920). Blood is taken aseptically into a sterile flask or bottle from an arm vein of older children and adults convalescing from measles, about five days after temperature has become normal. From 8 to 10 ounces of blood is withdrawn, depending upon the size of the patient. This is allowed to coagulate and when the clot has separated the clear serum is pipetted off, usually the next day. Each lot of serum is tested for sterility by both aerobic and anaerobic cultures, and a Wassermann test is made. If urgently needed, the serum of one patient is used for protective injections. But if there is plenty of serum on hand, the serums from several patients are mixed, and this pooled lot is then distributed into small bottles and kept in the icebox until needed. After each handling of serum, cultures are made, and a final culture from the first and last bottles of each lot is made before storing in 5 c.c. containers with paraffin-sealed corks. No preservative has been added, as most of this serum is used within a short time. If it is to be kept for any length of time, 0.25 per cent. tricresol could be added, as is done with other serums. This serum is given with a hypodermic syringe deep into the thigh muscles in

doses of from 5 to 10 c.c. depending upon the age of the patient and the time since exposure. In some cases in which there was intimate and continued exposure, a second dose a week or ten days later has been given, but a single early dose usually protects. In two cases, doses of 35 and 40 c.c. of the serum were given on the first day of the measles eruption in the hope of modifying the infection. The course of the disease did not appear to be altered by the injections.

The main use of the serum seems to be limited to prophylaxis against measles when given within the first week of exposure. This protection is apparently a passive immunity; and its duration is limited, apparently, to two months. The use of convalescent serum is further limited by the supply of serum. If each physician having under his care a measles patient over 10 years old would send the patient to the hospital laboratory for the drawing of blood, five days after the temperature had become normal, there could soon be collected a considerable amount of convalescents' serum. This could be distributed to the attending men of the hospital for use as needed. It is felt that the cooperation of the general practitioner in this way could be of great value in reducing the measles morbidity in young children, and this in turn would undoubtedly cut down the mortality rate, especially in children under five years of age.

Blood or serum from an adult who has had measles in early life has also been used with some success. While the protection afforded does not appear to be as great as that from serum taken during the stage of convalescence, this method might be advantageously used by practitioners if no other serum was available.

Abraham Zingher[7] also concludes that measles convalescents' serum, plasma or whole blood has definite value in the prophylaxis of measles. It can be used to produce complete passive immunity if injected within the first four or five days after exposure, and a mixed form

(7) Jour. Amer. Med. Ass'n., April 12, 1924.

of immunity if injected in larger doses after the fifth day. It can be injected in small doses after the fifth day of exposure to modify the character of the disease rather than to prevent its development. If an attack develops, the immunity will probably be permanent. The dose of serum during the first four days of exposure is 2.5 c.c.; during the fifth and sixth days, 5 c.c., during the seventh and eighth days 7.5 c.c. To influence the type of measles so that a modified attack of the disease will develop, the dose is from 2.5 to 3 c.c., injected from the fifth to the tenth day after exposure. These doses are calculated for children 3 years of age; they should be proportionally higher for older children and for adults.

When prepared convalescents' serum or plasma is not available, one should inject, intramuscularly, whole blood, citrated or not citrated, in double the amounts recommended for serum. The supply of convalescents' blood being bound to remain limited, the great value of recovered serum and of adult serum should be appreciated, as it can be obtained from parents or from other relatives. This supply is constant, always on hand and easily obtainable. The dose of these serums is about two to three times as large as that of convalescents' serum.

Complete passive protection with convalescents' serum or plasma has its field of usefulness in protecting very young and feeble children and those suffering from rickets, tuberculosis, diphtheria and whooping-cough. Also, during the cold seasons of the year, when catarrhal conditions prevail and there is danger of pulmonary complications, such complete immunization is often indicated. In private practice, however, in dealing with normal healthy children who have been exposed to measles, as well as in some institutions taking care of healthy robust children, it will be generally more desirable to use convalescents' serum, the serum of recovered cases or adult serums, so as to obtain a modified and mild form of the disease. A fairly permanent immunity

will thus be established, rather than a temporary protection for a short period of time.

Varicella Antiserum

Varicella Convalescents' Serum in Prophylaxis. A. A. Weech[8] reports nine infants exposed to varicella who were given from 3 to 4.5 c.c. of convalescents' serum intramuscularly within from one to six days after exposure. Eight of them did not contract the disease. In the ninth infant an extremely mild attack developed after an unusually long incubation period (22 days). The serum used was obtained from children in whom the disease had developed from ten to twenty days previously.

Though under ordinary circumstances, an attack of varicella is so mild and the sequelae so few that prophylaxis has not been considered a matter of great importance, any method of preventing the occurrence of secondary cases and diminishing the period of quarantine is of value in hospital practice, in which the long incubation period means a ward under quarantine for from 23 to 24 days.

Influenza Antiserum

Influenza Convalescents' Serum. L. Weise[9] reports success from the intramuscular injection of Influenza Convalescents' Serum prepared by himself. He administers from 5 to 10 c.c. intramuscularly and finds that in all patients the subjective sensations are remarkably quickly relieved and the fever is lowered, in some suddenly and others gradually. The fact that the epidemic in which he used the remedy was rather mild and that patients who were not treated were quite as free from complications as those who were lessens, somewhat, the value of his report. The suggestion is worthy of more extensive trial in future influenza epidemics.

(8) Jour. Amer. Med. Ass'n., Apr. 19, 1924.
(9) Klin. Wochenschr., Oct. 1, 1923.

Poliomyelitis Antiserum

Poliomyelitis Antiserum. Floyd Clarke and Andrew G. Dow[1] report six cases they were able to diagnose early, before the onset of paralysis, that received one or more injections of Rosenow's antiserum, in every one of which recovery was complete without paralysis. It is important that the physician have the disease in mind from June to November in each year, that every case of slight illness in children be regarded with suspicion, and that careful clinical search be made for a possible poliomyelitis. The most important single diagnostic sign is neck rigidity. The next most pronounced symptom in the early cases is a hyperesthesia, and a certain resistance of the child against examination and the necessary manipulations. The occurrence of paralysis should not be regarded as one of the early manifestations of the illness. If it occurs, it is usually a late symptom.

Pneumococcus Antiserum

Pneumococcus Anti-Serum in Lobar Pneumonia. A. I. G. McLaughlin,[2] using antipneumococcal serum Type 1, prepared by Burroughs and Wellcome, in 27 cases of lobar pneumonia, of which fourteen were Type 1, four were Type 2, and six belonged to Group 4, finds that the Type 1 antipneumococcal serum has a beneficial effect on pneumonias caused by other types of pneumococci, but not so marked as the effect on Type 1 pneumonias. Serotherapy seems definitely to diminish the incidence of post-pneumonic empyema. The best results are obtained when the serum treatment is instituted early in the disease, preferably before the third day. The initial dose of antipneumococcal serum should be 100 c.c. injected intravenously.

"As soon as the patient was admitted to hospital and the diagnosis established, inquiry was made concerning

(1) Jour. Amer. Med. Ass'n., Aug. 9, 1924.
(2) Lancet, Oct. 4, 1924.

previous injections of serum. When a history of previous injections was obtained, 1 c.c. of horse serum was injected subcutaneously to determine the presence or absence of protein sensitization. If no local or general reaction occurred within an hour, 50 to 100 c.c. of antipneumococcal serum were injected intravenously. This was carried out before the result of the sputum investigation was known. When Type 1 pneumococcus was found in the sputum the injections were repeated every eight hours until the temperature fell to normal and the pulse-rate dropped below 80. If pnemococci belonging to other groups were found, the injections were sometimes continued to observe the effect, but usually they were discontinued. The quantities injected ranged from 50 to 400 c.c.

"The apparatus consisted of two funnels, for serum and normal saline respectively, united by rubber tubing to a Y-shaped glass tube, which, in turn was attached to the infusion needle by another piece of rubber tubing. The needle was introduced into the vein, and about 5 c.c. of warm saline allowed to enter the vein, followed by a few drops of serum (warmed to 100° F.) mixed with a further 5 c.c. of saline. After waiting two or three minutes, 5 c.c. of well-diluted serum were injected, followed by another interval; then 10 c.c. of diluted serum were run in. If no untoward symptoms occurred after these tentative doses the undiluted serum was then injected slowly. In using this method, recommended by Cruveilhier, no anaphylactic phenomena have been observed. In one case, in which the serum had not been diluted, symptoms of anaphylaxis occurred during the administration. The symptoms rapidly subsided three minutes after the subcutaneous injection of 1 c.c. of pituitrin.

"After each injection the temperature fell at least two degrees, and in some cases became normal or subnormal. Concurrently, the pulse-rate and respiration-rate were lowered. As the effect of the previous injec-

tion began to wear off the pulse-rate increased, followed by a rise in temperature. Another injection of serum again caused the temperature and pulse-rate to fall. An increasing pulse-rate was taken as an indication that more serum was needed. After the temperature and pulse-rate became normal no more serum was given. In two cases, admitted on the second day of the illness, an intravenous injection of 100 c.c. in each case caused an instantaneous drop in the temperature with no secondary rises. No more serum was required, as the attack appeared to be definitely aborted. Both were definite cases of pneumonia."

Arthur L. Bloomfield[3] likewise concludes that Type 1 antipneumococcus serum is of real value; and that the occurrence of bacteremia in relation to the day of disease affords an index for prognosis in lobar pneumonia. As long as the blood culture is negative, spontaneous recovery is possible in the majority of cases. In the present series, the percentage of recoveries of patients treated with serum at a time when the blood culture was negative was 100, regardless of the day of disease. Bacteremia in the majority of instances of lobar pneumonia indicates, on the other hand, a type of reaction which is lethal despite serum therapy, although undoubtedly certain cases in this group can be saved as well.

Pollen Antigens

Pollen Protein Mixtures in Autumnal Hay-Fever. Harry S. Bernton[4] cites clinical and biologic evidence that there is no chemical identity of the pollen proteins existing in the short and giant ragweeds. The cross-protection afforded by active immunization with the pollen protein of the short ragweed against the giant ragweed is nil in subjects very sensitive to gaint ragweed, and light to those less sensitive. The author be-

(3) Jour. Amer. Med. Ass'n., Oct. 27, 1923.
(4) Ibid., May 3, 1924.

lieves that addition of pollen extract of giant ragweed in the preventive treatment is likely to afford autumnal hay-fever subjects greater protection and assure a greater freedom from symptoms.

Asthma Antigens

Autogenous Vaccines in Asthma. William S. Thomas, L. W. Famulener and Miximin DeMouy Touart[5] believe that, by means of preliminary skin testing, properly conducted, vaccine therapy may be put on a firmer footing; that by this method it may be possible to decide which of several autogenous vaccines should be used in treatment; or whether any vaccines should be used. False hope of cure by autogenous vaccine treatment in cases which show no positive reactions may thus be averted. Of 62 patients suffering with asthma so treated, 53 have been either completely relieved or materially improved.

Before considering the advisability of treatment with vaccines, the authors subjected all patients to a physical examination and to cutaneous tests for hypersensitiveness to foreign proteins. Where such hypersensitiveness was demonstrated in apparent causal relation to the asthmatic condition, an effort was made to separate the patient from the offending protein, or, when indicated, to desensitize him. In many instances surgical treatment was obtained for gross obstructions in the nasal passages and nasopharynx, and for infected nasal sinuses, tonsils and teeth. In addition, some form of medication was prescribed, and some of these patients were put to bed, at home or in the hospital.

During this preliminary period of observations and of symptomatic or specific treatment, which was rarely shorter than two weeks, a considerable number of patients were relieved of their asthma, and consequently did not receive vaccine treatment and are not included in this series. The remaining sixty-two cases were tested

(5) Arch. of Int. Med., July, 1924.

with autogenous vaccines and received therapeutic inoculations in accordance with the results of those tests.

In the preparation of test vaccines, cultures were made from various sources, depending on the indications in each particular case. Where sputum was obtainable it was always used, as was also aspirated material from infected accessory nasal sinuses. Cultures were sometimes made from excised tonsils and directly from the nares, pharynx, and the tonsils in situ. In certain instances, either because of some clinical indication or because of falure to obtain positive reactions with bacteria from other sources, cultures were made from the stool.

All organisms recovered from every source were made into vaccines, and with these vaccines intracutaneous tests carried on. Vaccine treatment was begun as soon as possible after decisive information had been obtained from the tests, usually from three to five days. Occasionally, only one organism was chosen, but it more often happened that two or more gave sufficiently active reactions to be included. The treatment vaccines were separate suspensions of each organism in physiologic sodium chlorid solution preserved by 0.25 per cent. tricresol, each cubic centimeter containing approximately one billion organisms. With some of the more toxic bacteria, notably *Streptococcus hemolyticus* and the Friedlander bacillus, the treatment dilution was reduced to five hundred million organisms in each cubic centimeter. The advantage in administering each type of organism separately is that it is then possible to judge accurately its effects by the size and severity of the local reaction.

In this method of vaccine therapy the purpose has been to produce in healthy tissues, at frequent intervals, a local reaction characterized by slight swelling and tenderness, and perhaps erythema of the overlying skin, lasting from one to five days. If the dose produced such a local reaction it was repeated at intervals of two to three days until none followed. In the event

of failure to produce a local reaction, or when a previously sufficient dose ceased to cause such a reaction, the amount was increased by one hundred million organisms on each occasion until the desired result followed. It seldom happened that the dosage exceeded four hundred million organisms at any time. As the asthma improved, the interval between doses was increased, first to five and later to seven days. Rapid and uninterrupted recovery occured in a few patients, but the usual course was gradual improvement, varied from time to time by exacerbations of the asthma. In most of these patients, vaccines were discontinued as soon as relief of symptoms and physical signs occurred. Finding, however, an occasional tendency to relapse after an interval of weeks or months, the more recent patients have been treated with weekly, bi-weekly or monthly doses long after the occurrence of clinical relief. The prolonged use of vaccines appeared to prevent relapses. Where symptoms continued unabated after six or ten inoculations, fresh cultures were made, at times disclosing the presence of organisms hitherto undiscovered.

The important factors in the use of vaccines seem to be, (1) proper selections by intracutaneous test; (2) preparation of each organism in a separate vaccine; (3) the use of a dose just sufficient to produce a mild local reaction; (4) adherence to this dose so long as it continues to produce such a reaction, then increasing it; (5) frequent dosage early in the treatment with a gradually lengthened interval, followed by (6) prolonged administration at relatively long intervals.

The clinician, in the physical examination of his patient, should search for all possible foci of infection. Material from infected foci should be collected and submitted to the bacteriologist for the isolation and identification of organisms present. Great care should be exercised to exclude extraneous contaminants and an aseptic technic is essential in all cases. Nasal dis-

charges may be collected with sterile cotton swabs, or, if copious, in sterile gauze wipes. Tonsillar exudate or pus may likewise be collected on sterile cotton swabs, care being taken to prevent contamination with saliva. If it is impracticable to make cultures at once, the swabs containing the material should be replaced in the sterile test tube, plugged with a sterile cotton stopper and sent to the laboratory to be immediately cultured. Sputum or feces should be collected directly in sterile jars and placed on ice if it is impossible to culture at once. In private practice, material collected on sterile cotton swabs may be seeded at once on the surface of solid culture mediums (blood agar slants and Loeffler's serum medium) and sent immediately (with collecting swab in sterile plugged test tube) to the bacteriologic laboratory for examination.

It is essential in the bacteriologic examination of specimens that a careful study of stained films of the original material be made as a guide to the bacterial flora present, and that it be cultured on special or enriching mediums, as indicated. The study of stained films of the original material offers a means of determining whether or not all types of organisms present develop later in the cultures. If not, further attempts should be made to culture and isolate all organisms that were found in the original material. The recurrence of symptoms in a treated case, after a quiescent period, calls for a repetition of the full bacteriologic examination in order to determine if infection with other types of organisms has supervened.

As a routine laboratory procedure, the materials are cultured directly on human blood agar slants and in dextrose nutrient broth. Also, a portion is emulsified in broth from which seedings are made by the dilution method in a series of poured blood agar plates. Without going into full details of the technic of culturing and killing organisms usually employed in the preparation of a bacterial vaccine, it is sufficient to state that

the organism is ordinarily cultured either on plain nutrient agar slants or in dextrose nutrient broth, dependent on the particular species. Ultimately they are killed by heating for one hour at 60°C., or at 65°, if necessary.

The standardization of the vaccine is based on the method published by Hopkins (1913), which offers a means by which an accurate measurement by volume of the thoroughly packed moist organisms may be made in a special type of centrifuge tube. A 1 per cent. suspension in physiologic sodium chlorid solution is prepared from the measured packed bacterial residue; then the organisms are killed by heat. Controls for sterility are made, after which sufficient tricresol solution is added to give a 0.25 per cent. concentration. A unit valuation has been placed on the volume content of bacterial substance present in such a suspension. The unit consists of that amount of bacterial substance which is present in 0.01 c.c. of a 1 per cent. suspension of the organism prepared under certain fixed conditions. Experience has shown that this quantity (1 unit) of vaccine is, perhaps, the most favorable amount to produce a skin reaction when applied intradermally in the hypersensitive patient. The 1 per cent. suspension of killed organisms, prepared by the Hopkins method, is designated "vaccine stock," and is supplied in small ampules for the intradermal tests. The vaccines for therapeutic purposes are prepared from the "vaccine stock" which contains 100 units per cubic centimeter. Dilutions in physiologic sodium chlorid solutions containing 0.25 per cent, tricresol are made to include the number of units per c.c. desired by the clinician.

Each test injection is made with a freshly sterilized tuberculin syringe and a needle of fine caliber, with which the control solution and each vaccine are introduced intradermally, so that minute wheals are seen.

The amount of test vaccine used in each instance is regularly 0.01 c.c. The scratch or dermal tests made with so-called proteins prepared from bacteria have been tried and have been found to be unsatisfactory.

As a control, in each series of tests, the same dilutent of sodium chlorid and tricresol solution is used as that employed in diluting the vaccines. The injections are made in a row, usually on the arm or forearm, which traverses the limb in a spiral direction, the distance between the points being at least 1½ inches. The oblique line is preferred because of the occurrence, in about 4 per cent. of the cases, of a reaction severe enough to cause a transitory lymphangitis producing a pink flush extending for several inches up the limb.

The positive reactions following these tests are of two separate types, (1) an early reaction, appearing in from ten to thirty minutes and soon thereafter fading. It is a wheal at least 1 cm. in diameter, with pseudopodia or grossly irregular outline, sharply marked off from a surrounding pink areola. (2) A late positive reaction, noticeable in twelve hours or less, and at its height on the second day. It persists for from two to five days, and, under certain circumstances, for several weeks. The reaction is not unlike the Schick reaction in appearance, but in order to read and interpret its significance, the component features must be noted by touch as well as by sight, and recorded graphically as they change from day to day. Positive reactions, whether early or late, are considered to be of equal importance as indications for the therapeutic use of the vaccines which produced them.

In reading and recording the early reactions, the circumference of the wheal is outlined on the skin with pen and ink, and numbered. When dry, this picture is transferred to wet blotting paper laid on it (Fig. 11) and later filed for record.

A negative skin reaction to an autogenous vaccine is taken to indicate that the organism is innocuous to its host. However, vaccines made of organisms

Fig. 11.—Early (half hour) reactions, as recorded. Organisms: (1) control; (2) atypical gram neg. coccus; (3) micrococcus albus; (4) pneumococcus type IV; (5) streptococcus hemolyticus; (6) streptococcus viridans No. 2; (7) streptococcus viridans No. 3.

commonly considered to be nonpathogenic have often produced positive skin reactions, and when used in treatment have given relief of symptoms. It is evident, therefore, that test vaccines should be prepared from all types of organimsm recovered from the patient.

NON-SPECIFIC TISSUE STIMULATION

Distilled Water

Intravenous Injection of Distilled Water. William J. Schatz[6], as a result of experience in 600 cases, considers intravenous injection of distilled water in doses varying from ½ to 5 c.c. entirely safe and

(6) Amer. Med., April, 1924.

valuable in a number of pathologic conditions. Intramuscular and subcutaneous injections of water, where the intravenous procedure was unachievable, as in infants, also gave results similar to those afforded by the intravenous injections though less certain, complete, and decisive. The pain element caused by the subcutaneous injection, moreover, made it impracticable. Compared with the negligible and momentary pain met with in the intravenous procedure, due to the introduction of the needle only, that attending intramuscular injections is considerable.

The dose has to be regulated in accordance with the sensitiveness of the patient. Hypersensitive are cases of hay-fever and neuralgia, bronchial and cardiac asthma, advanced tuberculosis and late syphilis. In these 1 to 1.5 c.c. seems a safe average dose. Sensitive are cases of neuritis, the toxemia associated with goiter, severe toxemia and vomiting of pregnancy, hemolytic manifestations, hypertension in phletorics, and fever. For these 2 to 2.5 c.c. is a proper dosage. In non-sensitive or tolerant cases 3 to 5 c.c. appear to be safe average doses.

Repetition of doses, with few exceptions, was practiced once a week. These exceptions applied to disorders in which improvement signs were evident, or in which intensification signs were obvious or induced within a very brief period after the dose. In these instances the greatest progress was observed when the doses were not repeated while improvement persisted. Aggravation subsequent to a well-defined beneficial response, however, was a sign for repetition.

The method evolved and used is somewhat similar to that employed in active immunization through injection of vaccines or pollen extracts. In both methods certain small doses do good, while larger ones fail or do harm. The water injection, however, has been regarded as a device which, through the induction of osmotic phenomena principally, effects a rearrange-

ment, in amount proportionate with the size of the dose employed, of biochemical constituents within the blood, whereby the same or a similar principle of therapeutics is involved.

In two cases in which large dosage had been employed fever appeared. Three cases known to be suffering from fatigue wastes experienced considerable languor following large doses. Therapeutic effects came gradually as a rule, although there were a few instances of startling decrease in symptoms. Decisive improvement within two or three days was achieved in about half of the cases of hay fever and neuralgia and in a considerable number of cases of vomiting of pregnancy, neuritis, and asthma. Complete relief within two or three weeks was quite the rule in these cases, with the exception of asthma. Here the time involved was usually a matter of months. Where symptom intensification was induced in these cases it appeared within a few hours, and in some instances persisted a number of days.

While pollen injections possess distinct preventive merit, the water injections demonstrated no real preventive value, but were followed by complete relief in practically all patients who came for treatment when their suffering was upon them during the active season. Symptoms of pertussis practically disappeared within three weeks as a rule. In about one-third of the cases the day cough had stopped within seven to ten days.

Notwithstanding evidence of focal infection, prompt relief from neuralgia was almost uniformly achieved. In those cases coming for treatment where eradication of foci had brought no relief even after considerable time, the water injections succeeded in every instance.

In eczema, psoriasis, and acne, the improvement came almost imperceptibly, and recurrences were the rule unless the injections were continued several

months after the skin manifestations had disappeared. The discomfort in angioneurotic edema and herpes zoster was relieved within about two days, although the lesions remained for one to three weeks.

Relief came very slowly in chronic rheumatism and rheumatoid arthritis, the deformities being practically unaffected. But the discomfort was reduced about 50 per cent., on the average, at least.

In vomiting of pregnancy, the beneficial results appeared somewhat more slowly, as a rule, than with injections of corpus luteum. Success, however, followed in two cases of toxemia in which the latter injections had failed.

In acute localized infections improvement of the general symptoms was experienced within twenty-four hours, as a rule. Except for decreased sensitiveness of noticeable degree, the focus revealed nothing in the same period. Combined with other treatment, the progress was very rapid.

In diabetes mellitus cases, though no direct effect upon the amount of urinary or blood sugar was traceable to the injections, the physical condition of the patients improved noticeably in nearly all cases.

The toxemia associated with goiter was beneficially influenced in all cases.

The effect of injections on the blood was that the coagulation time was reduced almost invariably within twenty-four hours after injection. An eosinophilia was either instituted or increased within the same period after the first injection; the average, however, being 0.686 per cent. only. The other white cells showed nothing typical. The hemoglobin was increased 2.62 per cent. within twenty-four hours after the first injection and gradually increased to 5.3 per cent. within 20 days, with three injections. The red cell count increased 113,480 on the average within twenty-four hours after the first injection, and increased to 122,000,

on the average, with three injections in 20 days. Only three cases in which the red cell count decreased received substantial clinical benefits. Of the others, eighteen had doubtful results. Cases with a count below 3,000,000 received little or no benefit.

In its mode of action "the distilled water causes, (1) an artificial hemolysis of a number of red corpuscles proportionate with the volume of water injected; (2) the substances thus liberated into the plasma, reacting with others present or secreted therein by certain leucocytes, endow the blood with antitoxic and bactericidal, though non-specific properties.

"This biochemical immune process accounts for both the favorable and unfavorable results obtained. The best of these were observed where the immunizing process could most readily exercise its influence; toxemias of endogenous or exogenous, metabolic or bacterial origin in which organic lesions were absent or very slight. This includes, for instance, the toxic neuroses (hay-fever, bronchial asthma, the neuritides, vomiting of pregnancy, etc.); toxic dermatoses (urticaria, angioneurotic edema, eczema, dermatitis venemata, etc.); and various milder infections (pertussis, bronchitis, rheumatism, and the exanthemata, etc.), before complications occur.

"Conversely, indifferent or negative results were obtained in severe infections in which the pyogenic organisms were of a virulent type (carbuncles, boils, tuberculosis, syphilis, etc.) because a sufficiently active reaction could not be provoked; also in organic functional diseases with destructive lesions (advanced tuberculosis, cancer, sarcoma, diabetes mellitus, etc.) for the same reason and owing to the lack of influence upon the lesion *per se*; also in toxic neuroses attended with trophic disturbances or changes (migraine, chorea, epilepsy, goiter, etc.) because of inability to influence these conditions.

"Reduction of coagulation time was due to liberation in the blood stream of prothrombin from the ruptured red corpuscles."

In the light of this interpretation it would seem that *intravenous injections of distilled water are indicated in uncomplicated toxemias or infections of a nonvirulent type, to initiate, and perpetuate by repeated injections, a defensive process of a non-specific type.*

Alcohol

Alcohol Injections. B. Spiethoff[7] uses intramuscular injections of from 0.1 to 0.3 c.c. of absolute alcohol, in sterile water to bring the amount to 1 c.c., at intervals of from one to four days according to the focal reactions, the same results are obtained as with parenteral protein therapy in trichophytosis, furuncles, cellulitis, gangrenous infectious processes, some forms of tuberculosis, psoriasis and gonorrheal complications. Pain occurs only at the moment of the injection.

Sulphur

Sulphur in Arthritis Deformans. Hobart A. Reimann and George W. Pucher[8] report results of sulphur treatment in seventeen cases, of which four showed marked improvement, four showed slight improvement, and the remainder were either not benefited by the treatment or became actually worse.

The preparation used consisted of flowers of sulphur, 7 mgm. to 1 c.c. olive oil, free from fatty acid, and sterilized at 150° C. for two hours. Longer heating was avoided, as it turns the solution to a deep red color due to the reaction of the sulphur with olive oil or some of its decomposition products. The final product, as used, was a clear, golden yellow liquid.

(7) Münch. Med. Wochenschr., June 13, 1924.
(8) Amer. Jour. Med. Sci., July, 1924.

The character of the reaction varied. Some of the patients showed no increase of temperature, even following doses of 6 c.c. (42 mgm.). Most of the patients, however, responded with nausea, vomiting, chills, restlessness, general joint pains, and severe headache. The headache was often relieved by pyramidon. Simultaneously with the constitutional reaction there is an increase in the polymorphonuclear leukocytes (up to 24,000). With the larger doses of sulphur, there was severe pain at the site of injection, lasting for several days. The pain in several cases was so severe that it required the administration of sedatives. That all these phenomena were not due to the action of olive oil was shown by the fact that control injections of olive oil by itself produced no reaction.

They could not entirely confirm the chemical data of Meyer-Bisch. There was no reaction in urine volume or chlorid excretion, and they have not been able to confirm the observation that sulphur injections cause excretion of substances giving the reaction of conjugated glykuronates.

They conclude that only those patients were favorably affected by the sulphur injections who showed, radiographically, no organic obstruction to the joint motions. The other patients, in spite of cooperation and favorable psychic influence, showed no improvement whatever; so that it is evident that sulphur cannot be looked upon as a remedy for the latter class. They believe that it is not impossible that the remedy will find its place among others for the treatment of the former kind of joint affections.

It is, however, another question whether the action of the sulphur in these cases is a specific one. A number of other substances, as is well known, have been used for the treatment of arthritis, as, for instance, injections of milk, sanarthrit, proteogen, and vaccines, all of which have been used, according to

some observers, with favorable results. All of these substances call forth a reaction on the part of the organism very similar to that of injected sulphur, although not as severe. Such results, it is accepted, are to be ascribed to the absorption of foreign proteins. The injection of sulphur, especially in larger doses, produces a violent local reaction, with necrosis of muscle tissue and an acute inflammatory exudate extending far beyond the point of injection. Of this the authors have been able to convince themselves during the course of their experimental study on animals. Absorption from the site of injection may then be responsible for the general reaction. In that case, the action of sulphur would be analogous to that of non-specific proteins with increase and mobilization of the leukocytes which may be accompanied by the mobilization of the proteolytic ferments.

Robert Meyer-Bisch[9] contributes a further report on sulphur injection treatment in chronic polyarthritis, which he believes to act similarly to protein injections but to be superior to them. The latter are subject to marked variations in composition and are liable, by reason of their protein content, to give rise to anaphylactic phenomena. Furthermore, some cases are not improved by protein therapy. Sulphur injections produce a similar effect, and in addition probably have a specific action on joint cartilage, as brought out in a previous article (cf. This Series 1922, volume 6, page 49).

In the present communication the author reports that he is able to obtain perfectly satisfactory results with the use of a 1:1000 solution of sulphur in oil, and that a dose of 3 to 5 mgm. produces a change in the leukocyte picture and therapeutic results without much fever. Only rarely is it necessary to use the 1 per cent. solution. The sand-bath is a useful adjunct to

(9) Die Erkrank. des Bewegungsapparates, January, 1924.

this treatment, most especially at the time of the most marked focal reaction of the joints, *i. e.*, generally on the second day after the injection.

Erich Meyer* also finds sulphur oil useful in chronic non tubercular diseases of joints. He has been using a colloidal sulphur preparation (Sufrogel, Heyden). If the first two injections are without result further treatment offers no prospect of improvement. After five or six injections further improvement is, as a rule, not to be obtained.

Sulphur Injection in Arterial Hypertension. Stefan Rusznyak[1], having made the accidental observation during the treatment of chronic polyarthritis, that sulphur injections caused a lowering of blood pressure, most especially during the febrile reaction, but lasting for days thereafter, employed this method of treatment in about 50 cases of arterial hypertension, using a 1% sulphur solution, marketed under the name of "Sulfolein" (Egger), in doses of 1 c.c., increasing gradually, in accordance with the febrile reaction and the course of the blood pressure curve, to 3, 5, 7, and even 10 c.c. at intervals of three to five days. He gives, alongside of this, 0.5 gm. of barbital by mouth every evening.

He concludes that sulphur injection is a powerful remedy for the relief of arterial hypertension and its consequences such as circulatory cerebral disturbances (pseudo-uremia, dizziness, paresis), visual disturbances, albuminaria, etc. As to the mode of action of this treatment, the author believes that, in consequence of the vaso-dilatation occurring during the fever, the peripheral vascular spasm is abolished and, thus, a vicious circle broken into. He bases this view upon the lack of effect of sulphur injections upon normal blood pressure and the usually prolonged depression of blood pressure following the treatment. He regrets

(*) Klin Wochenschr, No. 49, 1923.
(1) Klin. Wochenschr., Feb. 12, 1924.

the painfulness of these injections and believes that the development of a painless sulphur preparation would constitute an important step in advance in therapeutics.

Colloidal Sulphur to Lessen Local Reaction. J. Dengler[2] has been studying a colloidal sulphur preparation, "Schwefel-Diasporal," prepared by Volkmar Klopfer, Dresden-Leubnitz, and finds that by means of its intravenous injection one may obtain the same therapeutic results as by intramuscular injection of sulphur oil without the very distressing local manifestations of the latter. He begins with 1 mgm. doses and increases gradually to doses as high as 10 mgm., the injections being given at intervals of three to six days, always after the disappearance of the previous reaction. Among 14 cases of chronic joint diseases there were only two complete failures; in nine of the patients there was considerable improvement, six were relieved of pain, four were discharged completely able to work, four others were partially able to work.

W. J. Monaghan and Frank Garai[3] have been using intravenous injections of a preparation they call "338 activated colloidal sulphur" in cases of acute and chronic polyarthritis, as well as in arthritis deformans and septicemia, with results so good that they ascribe germicidal powers to this preparation.

Sulphur Gelatin (Sufrogel). E. Meyer and R. Meyer-Bisch[4] have been using intramuscular injections of a very fine suspension of sulphur in gelatin ("Sufrogel"-Heyden, containing 0.3 per cent. of sulphur) and find that because of its fine subdivision ½ to 1½ mgm. of sulphur developed the same clinical effects produced by 3 to 5 mgm. of sulphur suspended in oil, and that the local reaction following the injections were much less severe. They commence with 0.2 c.c. and increase

(2) Klin. Wochenschr., Feb. 19, 1924.
(3) Med. Jour. and Record, July 16, 1924.
(4) Klin. Wochenschr., Dec. 3, 1923.

the dose to 0.3, 0.5, and even 1 c.c. given at intervals of 8 days, being guided by the severity of the reaction. Dry heat, most especially in the form of sand-baths, is a great adjuvant, especially on the day of the most intense focal reaction, which occurs one to two days after the injection. After five to six injections further improvement is usually not obtainable. If the first two injections are without result there is no prospect of improvement from continuance of this treatment.

Colloid Metals

Colloidal Metals in General Sepsis. George Heinrich Schneider[5] considers the intravenous injection of colloidal metals an important and insufficiently appreciated enrichment of our remedial measures in the treatment of bacteremias, the most important factors for success being sufficiently early commencement of treatment and sufficient dosage. He reports twelve cases of grave bacteremia, mostly the result of septic abortions, nine of which recovered and three died. In eight of these cases positive blood cultures were obtained.

The author has employed aurocollargol or cuprocollargol-Heyden in doses of 20 c.c. slowly injected into the vein and repeated daily as long as necessary. These doses can be safely employed in view of the minute quantity of metal employed in these solutions. Paravenous injections must be carefully avoided as these solutions are irritant. Adherent particles of solution should be wiped from the needle before introducing it under the skin. The intravenous injection succeeded so often in aborting an approaching chill that the author feels convinced that it must have exerted an influence upon the organisms circulating

(5) Klin. Wochenschr., Aug. 26, 1924.

in the blood. He admits that a general cellular stimulation such as is obtained in proteotherapy may also be of importance in explaining the effect.

Milk

Proteotherapy in Disease of the Motor Apparatus. R. Schmidt[6] formulates the proposition that a chronic inflammation can heal only by way of an acute inflammation. This apparent paradox he explains by the supposition that the equilibrium between assimilation and dissimilation is disturbed in favor of assimilation in chronic torpid inflammatory processes accompanied by exudation and new formation of tissue. Through an increase in protoplasmic activity, both of these functions are raised in the focus of inflammation. This means increased inflammatory activity (focal reaction), the negative phase. In the further course the author assumes that the already constantly overworked assimilative function becomes exhausted and overbalanced by the less overworked dissimilative function which causes a recession of the inflammatory process, the positive phase.

This diphasic nature of biological reactions seems to be quite general. It is well illustrated by the particularly definite arthritic focal reaction following provocative injections, such as milk, tuberculin, etc., which is followed by a lessening of the painfulness and diminution of the swelling. The special reason for the value of the proteotherapy in diseases of the joints is due to the fact that torpid inflammatory processes are especially found in this system of organs. In general, this protoplasm activation is desired wherever there are evidences of a certain degree of torpor. The more torpid the inflammatory process and the more limited its localisation the greater the indication for proteotherapy, and

(6) Die Erkrank. des Bewegungsapparates, January, 1924.

vice versa; for another feature of the effect is probably to be found in arousing of the entire organism to better defense against a locally limited disturbance.

Combination of proteotherapy with the ordinary remedies seems to be frequently desirable, as an increase in the blood and lymph circulation of the infected part causes an increased determination of the remedy to the part. At least this is the best way to explain the advantage of simultaneous treatment of articular rheumatism with salicylate and milk injections, and of lues with mercury and milk injections. Schmidt found milk injections to increase the potency of thyroid in reduction cures.

As to the choice of a suitable preparation for proteotherapy, we suffer from an embarrassment of riches. The author has seen no reason to give up the use of ordinary milk, sterilized by boiling in the water bath for ten minutes. In milk we seem to have a fortunate combination of proteins with bacterial bodies (chiefly *b. coli* and a lactose fermenting streptococcus) which is exquisitely pyrogenic without great toxicity. The commercial ampules of milk preparations suffer in general from deficiency in pyrogenic action. The author sees therein no advantage but rather a disadvantage.

One should commence, in general, especially in those who have a tendency to strong febrile reactions (the tubercular, luetic), with small doses, *e. g.,* 0.5 c.c. of milk injected intragluteally. One should always wait until the reaction disappears. Inject therefore after three day intervals. The dose should always be so selected as to produce a moderate focal and general reaction. The average duration of treatment is about four weeks.

The Active Agent in Milk Injections. Otto Barkan and R. F. Nelson,[7] experimenting with guinea-pigs give the following results of experiments:

(7) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

Substance Injected	Maximum Rise of Temperature	Duration of Fever Over 1° F. Hours
Certified milk (cow's)	0.7	...
Whole milk (bacterial count, 300,000) cow's milk, noncertified	2.3	4½
Filtrate of whole milk (sterile)	1.8	2¾
Culture of whole milk (washed)	2.0	3
Washings from culture (sterile)	1.5	1½
Inoculated certified milk	1.9	4

They found parenteral injection of milk of low bacterial count (certified milk, 10,000 germs per c.c.) caused fever of 0.5° F. for one hour only. Milk of high bacterial count (whole milk, 300,000 germs per c.c.) caused fever of 2.3° F. This fever remained over 1° F. for four and one-half hours, and took nine hours to subside. That this difference in febrile reaction is due to bacterial action is suggested by the fever following an injection of a bacterial culture obtained from the whole milk, and is proved by the fact that certified milk when inoculated with bacteria from whole milk and allowed to stand for 24 hours gives the same febrile reaction as the whole milk. That, however, the constitutional reaction, for which the rise of temperature is taken as an indicator, is not due to the injection of bacterial bodies alone is shown by the less intense fever that follows an injection of; (1) the bacteria free filtrate from whole milk and (2) the sterile filtrate from the bacterial culture obtained from whole milk. The active agents in the washings must consist either of bacterial proteins or protein products which are the result of disintegration of bacterial bodies, or of an excretion (exotoxin) of the bacteria. The action of the whole milk filtrate must also be due to these elements, with the addition perhaps, of albumoses, proteoses, and peptones—the products of bacterial action on the native milk proteins themselves.

In the authors' opinion, the native milk proteins in themselves (in the amounts used clinically) are inactive.

Clinically, they have observed that as long as they could obtain only certified milk, the injection was practically valueless. In other words, *the "milk reaction" is not a milk reaction at all. It dependens on milk bacteria and the soluble parts of their metabolism, and not on native milk proteins.* If we wish to obtain a reasonably certain febrile reaction, and if we insist on milk for purposes of protein therapy, we should use only a milk of high bacterial count.

The authors will, in the future, use a more suitable and convenient agent than milk to elicit reactions.

Milk Injections Made Less Irritating. K. D. Graves[8] reports that the use of fat-free milk instead of whole milk has given splendid results, the local reaction being practically nil. Milk is centrifugated, and care taken to load the syringe with milk well below the cream line. It appears that the cream is undesirable, as it is absorbed slowly and acts as a foreign body instead of an absorbable solution.

Proteotherapy in Treatment of Pus Tubes. Weinzierl[9] employed Arthigon, milk, and caseosan in the treatment of about 300 cases of gonorrheal tumor of the adnexa. The author concludes that each of these is useful. Arthigon, given intravenously in doses of 0.2 c.c. gradually increased to 2 c.c., has a specific effect and is suitable for the differential diagnosis of ascending gonorrhea. It also produces more favorable results than the others in the subacute and chronic stage. Arthigon affects favorably gonorrheal cervical discharge, which is practically not at all influenced by the others. The author believes that the effect of Arthigon is strictly specific, and not merely that of proteotherapy.

Milk injected intragluteally in doses of 5 c.c. gradually increased to 10 has given better results in the acute stage than Arthigon, and also in non-gonorrheal tumors of the adnexa in which Arthigon failed completely.

(8) Jour. Amer. Med. Ass'n., Nov. 8, 1924.
(9) Zentralbl. f. Gynäk., June 7, 1924.

Caseosan intravenously in doses of 0.1 to 0.2 c.c. cautiously increased to 1.0 c.c. has given results similar to those obtained with milk and seemed particularly suitable for inflammatory processes occurring after abortion or delivery, especially in the early days of the puerperium.

Nuclein

Nuclein in Pneumonia. F. M. Gardner-Medwin[1] believes that, in the treatment of pneumonia, nuclein converts the watching rôle of the physician into one of active combat; and that other conditions exhibiting a leukopenia may respond to similar treatment. On the strength of the observation that the white cell blood count of cases of influenza is low and remains low after the fever has ceased, and for about five days after that, after which there is a sudden reactionary increase; and that an injection, either subcutaneously or intramuscularly, of sodium nucleinate in solution precipitates a reactionary increase of white cells in the peripheral circulation and so might reinforce the patient's resistance, the author has given intramuscularly sodium nucleinate solution (put up by the Clin Laboratories in ampules of 2 c.c., containing 0.05 gram per c.c.) in severe influenzal pneumonia, and seen counts rise from 3,200 to 18,300 three days after the injection, with corresponding improvement in the patient's condition from a practically moribound state to one of convalescence in the same period. As the toxic symptoms of many of the cases suggested an acidosis, intensive doses of sodium bicarbonate (2 to 4 gm. every four hours) were given either by mouth, bowel, or intravenous injection, together with glucose in the food or by bowel.

The success which attended the author's efforts in the pandemic period was so marked that since then he has invariably treated all cases of pneumonia on the same

(1) British Med. Jour., July 12, 1924.

lines. In every case of definite lobar pneumonia, a crisis has occurred about 48 hours or so after the first dose of sodium nucleinate was given, no matter what day of the disease it was administered. The cases of bronchopneumonia did not respond so typically as did those of the lobar type. They fell by lysis rather than crisis. If we eliminate from the series all the cases of bronchopneumonia (of which two died), and also all the cases which did not receive intensive alkaline treatment (4), we also eliminate all the fatal cases but two, which were moribund on admission and had chronic nephritis before contracting pneumonia. The author thinks it is worthy of note that in all the cases of lobar pneumonia, fully treated, the patient's condition began to improve at once after the nuclein injection, that all of them experienced a sense of well-being the next day, and that in every case the crisis occurred from 48 to 60 hours after the first injection of sodium nucleinate.

The accompanying diagram, Fig. 12, shows the length of fever of 40 successful cases of lobar pneumonia. The vertical lines represent the duration of the pyrexia, and

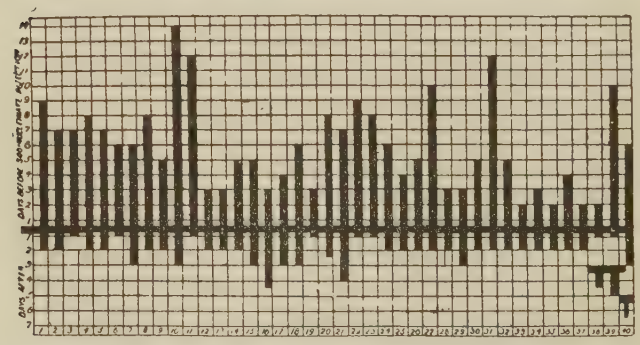


Fig. 12.—Diagram showing the duration of fever in forty cases of pneumonia treated by sodium nucleinate. Horizontal lines represent time of injection of sodium nucleinate; vertical lines show duration of fever. Cases 38, 39, and 40 show relapses with extension of pneumonic area, treated with a second dose.

the horizontal lines the nuclein injection, showing that the effect of the treatment in precipitating devolution is independent of the duration of the illness.

Peptone

Peptone and Vaccine Combined in Treatment of Asthma. John Veitch,[2] having found that certain cases did not react to peptone or vaccine when given alone, devised a system of giving a course of injections of peptone and vaccine combined in one solution. The solution used was in three strengths, as follows:

A. 5 c.c. of 5 per cent. solution = 0.25 gram peptone + 235 million organisms mixed catarrhal vaccine.

B. 5 c.c. of 10 per cent. solution = 0.5 gram peptone + 940 million organisms mixed catarrhal vaccine.

C. 10 c.c. of 10 per cent. solution = 1 gram peptone + 1,880 million organisms mixed catarrhal vaccine.

The injections were given every seven days: for the first four weeks half a tube of A solution per week, for the second four weeks half a tube of B solution per week, and so on, increasing in strength of dosage. The injections were given intramuscularly in the so-called painless area just below the anterior superior spine of the ilium, by means of an ordinary-sized serum needle, the needle being pushed in till the bone was felt, then slightly withdrawn and the contents of the syringe injected. On withdrawal of the needle the area was briskly massaged with a hard pad of cotton-wool to diffuse the fluid through the tissues.

A sharp reaction usually followed in about six to eight hours, there was some local redness and tenderness, and the temperature rose a degree or so. Further, there was a tendency to perspiration, but no other symptoms

(2) British Med. Jour., Jan. 5, 1924.

developed. The injections were given at night and the patient was able to be up and about the next day without discomfort. No special diet or medicinal treatment was indicated.

Of the 24 cases treated by this method fourteen were cured, four greatly improved, five slightly improved, and only one showed no improvement. In younger patients the signs of improvement were to be seen early. Age seemed to count more than the duration of the condition. As age increased the condition was more stubborn to treatment; but in some cases, prolonged exhibition of the combination gave satisfactory results. One of the cases after prolonged administration developed nephritis which cleared up after stoppage of treatment. All the cases gained in weight while under treatment and their general health was improved.

Snake Venom

Snake Venom "Crotalin" to Produce Non-Specific Protein Reaction. Ralph H. Spangler[3] has been using for the last fifteen years intramuscular injection of venom protein (crotalin) in over 600 cases to produce non-specific protein reaction, and he claims this to be one of the earliest recorded instances of the non-specific use of protein for therapeutic purposes.

Ten years ago clinical results of non-specific therapy were hard to explain. Specificity in medicine was at its height then, and any results obtained with protein injections were considered to represent pure empiricism and were diametrically opposite to expressed conceptions of immunity. Now, our knowledge of the specific factors of immunity is quite well established, but exact information of the non-specific elements is less definite. While specific immunization aims to influence directly the cause of the pathological process and is of great

(3) Med. Jour. and Record, Oct. 15 and Nov. 5, 1924.

value in conditions of known etiology, non-specific agents exercise their power by altering the reactivity of the whole organism through the production of two fundamental changes, *viz.*, general cell stimulation—plasma activation as Weichardt explains it—and alteration of the permeability of cell membranes as shown by Starkenstein and others.

Formerly the therapeutic effect was ascribed to the reactive leukocytosis that often follows many of the non-specific injections. Many investigators have found that this leukocytosis is frequently polymorphonuclear, and practically all have reported that it is usually preceded by a primary leukopenia. It has been frequently pointed out, however, that the therapeutic effect does not run parallel with the general leukocytosis produced Others have observed an eosinophilia after protein injections, suggesting some relation to the anaphylactic picture. Following intramuscular injection of venom protein no general leukocytosis is produced. There is, however, a decided alteration or modification in the proportional relation of the cells in the different counts for 48 or 72 hours following a venom protein injection, the most constant change being an increase in the percentage of eosinophile cells and a decrease in polymorphonuclears.

Snake venom belongs to the albuminoids and consists of two principal compounds, one a globulin and the other a peptone. The globulin element acts primarily on the blood and blood vessel walls. The clotting time of the blood is lengthened and the permeability of the vessel walls increased. In lethal doses of venom in animals, the blood is found to lose its power of coagulation and passes freely through the blood vessel walls into the surrounding tissues. The peptone element affects the nervous system and in large enough doses causes paralysis. Flexner and Noguchi found enzymes in venoms, *e. g.*, proteases and lipases.

The evaporated, dried, yellowish crystals, extracted from the *crotalus horridus* are disolved in sterile water and glycerin to which is added enough tricresol to preserve and keep the solution sterile. This solution is prepared in varying concentrations and put into sterilized ampules containing one c.c. each, representing 0.0025 grain, 0.005 grain, and 0.01 grain, etc. The injections are given alternately in the left and right forearm group of supinator muscles.

In the average patient there is but little cellulitis at the site of injection, and this usually reaches its maximum in from 24 to 36 hours. The injected area will usually return to normal in two or three days.

As a rule, venom protein injections, in doses ranging from 1/400 to 1/50 grain, produce no chill, fever, sweating, or other systemic disturbance. An increase in the number of erythrocytes in twelve, fourteen, or 36 hours following an intramuscular injection of venom protein has been a uniform finding. It has been the rule to note a slight leukopenia within the first six or twelve hours, and by 24 or 36 hours, to find the total number of white cells about what they were before the injection; never a leukocytosis. It is a routine rule to use the percentage of eosinophiles produced following an injection as a guide to the strength of the dose of venom protein as well as to the frequency of administration. The author has seen an increase of eosinophile cells to as high as 25 and even 40 per cent. with a corresponding reduction in the relative number of polymorphonuclears. Clinical experience seems to indicate that with crotalin injections in doses large enough to cause a biological reaction, following which not more than 8 to 10 per cent. of eosinophilia appears in the differential leukocyte count, we have an agent which produces a state of cell stimulation and altered permeability of cell walls corresponding to that stage in the mechanism of the nonspecific reaction which is of therapeutic value. This stage might be termed a preanaphylactic state.

As a rule, the highest percentage of eosinophiles, following the range of doses (1/400 to 1/50 grain) which the author has used, occurs by the second or third day. In from five to seven days after an injection, the eosinophile cells as a rule will again have dropped to 4 per cent. or under, and the patient may be given another injection. It has been his practice not to repeat an injection if the percentage of eosinophile cells by the fifth day has not dropped to at least 4 per cent. Moreover, it has not seemed wise to increase the strength of dose as long as any given strength is producing 8 to 10 per cent. eosinophilia on the second or third day after injection. When venom protein injections are given intramuscularly and are regulated by the percentage of eosinophiles in the differential leukocyte counts, they produce little local reaction and discomfort. Moreover, there is no shock or vasomotor paralysis and practically no disturbing systemic reaction. Chill, fever, nausea, and vomiting or depressing symptoms have been absent, and patients receiving crotalin injections on an average of once a week can attend to their routine occupations without the slightest inconvenience.

In an experience with the treatment of over 600 cases of epilepsy, the author has witnessed some striking therapeutic results following the non-specific reaction of venom protein. Venom protein has not relieved, or even improved, the convulsive symptoms in all of his cases, but in many of them. Independently of this, the effect of the venom protein injections on the general metabolism and health of the patient has been uniformly beneficial. It is the rule for the patients to gain in weight. The stimulation of the red bone marrow following crotalin injections increases the number of the erythrocytes. The hemoglobin percentage rises and the patient experiences a feeling of well-being which is very evident. The general resisting power of patients who receive venom protein injections is increased, and intercurrent illness is infrequent. Injuries and cuts as a rule heal promptly

without infection. Susceptibility to infection and contagious disease is lessened. Epileptic children who were receiving venom protein injections, exposed to scarlet fever, measles, chickenpox, or grippe did not contract the disease. Following the influenza epidemic of 1918, the author reported an observation made on 44 patients who had been receiving venom protein injections for three months or longer; 30 of them were directly exposed in the same house with one or more persons suffering with influenza, and yet only three of the 44 patients presented modified symptoms of the infection. In two other patients to whom one injection of venom protein had been administered, severe cases of influenzal pneumonia developed.

The author uses venom protein injections in conjunction with other drugs, *e. g.*, bromid or luminal in cases of migraine, periodical neuralgia, and arthritis; and he has seen the value of iodids, acetanilid, and the salicylates greatly enhanced by the adjuvant effect of venom protein.

The adjuvant effect of venom protein injections by its non-specific action in stimulating glandular and general plasma activation and by altering the permeability of cell walls often enhances the oral use of dried extracts of the glands of internal secretion.

The author submits that chemically, physiologically, and therapeutically venom protein (crotalin) solution seems to meet satisfactorily the requirements of a biological agent to produce non-specific resistance.

Coley's Toxin

Coley's Toxin in Treatment of Rheumatoid Arthritis. Inasmuch as, by protein shock therapy, the acute inflammatory arthritis of rheumatic fever, or the acutely inflammatory phase of rheumatoid arthritis can be definitely checked, inhibited, or temporarily put in abeyance, and as intravenous injections are not satisfactory, be-

cause a small dose may give a very heavy reaction, Robert Torrey and Thomas Klein[4] in looking for a substitute for intravenous medication, chose Coley's toxin, (prepared from cultures of a virulent streptococcus originally derived from cases of erysipelas combined with *B. prodigiosus*) and have found it satisfactory. This preparation had been used for many years in the treatment of sarcoma, and experience showed that it was constant in its action and toxicity. The preparation is relatively stable; and, injected intramuscularly, it causes a reaction very similar to the reaction obtained by intravenous injection. But the degree of reaction can be controlled by varying the dose. Experience in treating sarcoma has shown that repeated injections could be given satisfactorily over long periods of time.

Starting the dose at ¼ of a minim, it is increased by doubling the dose until a reaction occurs. The doses are given at intervals of two to five days at first; preferably about five days. At a five-day interval a given reaction can usually be approximately duplicated by an increase of 50 to 75 per cent. over the previous dose.

Focal reaction in the joint with increased soreness may occur after the first two or three injections. This rapidly disappears and a period of amelioration may be expected lasting at first for a day or two and increasing in length after each injection. The interval between injections may be increased to from seven to ten days. As the dose of toxin is increased to about 7 or 8 minims, a point is reached where little further tolerance is secured, and reaction to this dose seems about constant. Local reaction is marked as the dose increases, but focal reactions in the joint cease.

This method of treatment is successful in combating the acute inflammatory reaction in the joint. Contractures, which are responsible for most of the permanent

(4) Amer. Jour. Med. Sci., February, 1924.

deformity in rheumatoid arthritis, can be overcome surprisingly well by persistent effort, in most cases by some means of extension by weights. Baking is useful where fibrosis is a factor, and manipulation and massage by a skilled and careful operator are of great service. Of course, the first requisite of treatment is the eradication, so far as possible, of areas of chronic infection.

Diphtheria Antiserum

Non-Specific Reaction from Antidiphtheric Serum. As the result of clinical and experimental study of 91 cases, Ben Witt Key[5] ventures to predict that when protein effects are more clearly defined and understood, and protein preparations selected, perhaps for a specific reaction, the time will come when the accepted treatment of pneumococcic and staphlyococcic infection of the refractive media of the eye, in addition to local treatment, will consist in the administration of a foreign protein as soon as it can possibly be injected, just as now antitoxin is demanded immediately and in sufficient dosage in the treatment of diphtheria itself. He believes that *antidiphtheric serum, as it is now prepared, offers the best form of foreign protein for administration to the human.* Because milk varies in its potential and toxic action, numerous commercial preparations are now undergoing experimentation. Normal horse serum, "yatrencasein," albumose, proteose, non-specific vaccines, etc., have not as yet been shown to possess, with any certainty, a more reactive and potential effect than that of antidiphtheric serum. Furthermore, the dosage and reaction are quite uncertain. The dosage of the serum is certainly more definite and its anaphylactic effects are more clearly understood. Darier, Frogier, and others claim to have shown that it is ten times more potent than normal horse serum. Moreover, the theory as to the properties and structure of antibodies in

(5) Jour. Amer. Med. Ass'n., Jan. 19, 1924.

immunity lends striking evidence that there is a direct antagonist, a special antigen or protein (globulin), in the serum more active than a mere animal protein (milk, egg albumin), the method of concentration of the serum adding to the concentration of the antibody elements in the serum. If there is any virtue to be had in the non-specific diphtheritic elements (colloids?) in the serum, there is a decided advantage and preference in antidiphtheric serum over other forms of protein employed in this therapy. Furthermore, the facility of obtaining and administering suitable doses of antidiphtheric serum is a distinct advantage not to be overlooked.

History of previous anaphylactic conditions, previous diphtheria, status lymphaticus, asthma, or hay-fever-like attacks to persons proved susceptible in a stable and horse environment are well established as probable contraindications to serum injections. The author has not observed serious anaphylactic effects in any case, and doses have varied from 1,000 to 5,000 units and a total, in one case, of 12,000 units (given in 3,000 and 2,000 unit doses).

It is best, after cauterizing an active ulcer of the cornea, to have the serum injected as soon as possible. The effect of the serum is manifest always within from 24 to 48 hours after injection, the time of hypersensitivity and cellular reaction.

Malaria Inoculation

Treatment of General Paralysis by Inoculation with Malaria. Warrington Yorke and J. W. S. Macfie[6] report on malaria inoculation treatment of 105 patients with general paralysis. So far as can be judged at present, the results obtained with the treatment in general paralysis are most satisfactory. Of 84 patients observed for a sufficient time after treat-

(6) Tr. Royal Soc. Med. and Trop. Hygiene, March-May, 1924.

ment to warrant any conclusion, 27.4 per cent. have been, or are about to be discharged as provisionally cured; 20.2 per cent. have shown distinct mental and great physical improvement; and many of the remainder have improved physically. These cases have offered opportunity for the study of the mechanism of quinin action. The induced malaria infection has proved extraordinarily susceptible to treatment, a short course of quinin for three consecutive days being sufficient to sterilize the infection. These successes are in contrast with the frequent failures obtained in malaria in ordinary practice. Observations on the value of quinin prophylaxis have also been made, and show that administration of the drug before infection is useless; that its administration must be continued for at least ten days after the infection to prevent infection from developing; and that the daily dose given has but little influence apart from the fact that with very large doses (2 gm.) the period for which the drug has to be given to prevent development of infection is shortened a little.

Skin Irritation

Skin Irritation Increases the Bactericidal Power of the Blood. L. Colebrook, A. Eidinow and L. Hill[7] report experiments which tend to show that any "insult" to the skin, whether produced by ultraviolet and visible rays, by dark heat, or by blistering agents, provokes or increases the defensive powers of the body. Its immunizing properties are enhanced. This, the authors believe to be due to the absorption into the blood of the products of tissue damage, or the enhanced absorption of normal tissue products produced by such damage, which may be a natural excitant of immunizing reactions.

(7) British Jour. Exper. Pathol., April, 1924.

FUNCTIONAL THERAPY

CATHARTICS

In General

Administration of Purgatives. Walter C. Alvarez and B. L. Freedlander[8] used fifty small glass beads as an index to the rate of progress of the everyday food of the individual. Ordinarily, some 15 per cent. of these beads are passed on the first day; 40 per cent. on the second; 15 per cent. on the third; and 10 per cent. on the fourth day. After that, it may take days or weeks before the last few beads are recovered.

The most interesting fact that emerges from these studies is that the colon normally retains food residues from meals taken during the preceding week, or before. Ordinarily, about 80 per cent. of the residue from any one meal is extruded by the end of the fourth day. The rate varies markedly, however, in normal young men who have one or more satisfactory bowel movements every day. The essential point is that wide variations are perfectly compatible with good health. Theoretically, men with slow rates and well formed, well digested stools should have good health, and those with the fast rates and voluminous, mushy, badly digested, and frothy stools should have poor nutrition, flatulence, and indigestion. In office practice that is often true; but it is not a rule, because some people are so insensitive, or their factors of safety are so great that they remain oblivious to a high degree of intestinal indigestion.

The following lessons may be learned by the clinician:

(8) Jour. Amer. Med. Ass'n., Aug. 23, 1924.

When the colon is well cleaned out by a purge or by a large defecation, no bowel movement should be expected or demanded the next day. It will appear only if the colon is so sensitive that it can respond to the distention brought about by the food residues from one day.

If very little food is taken, as after an operation or during an illness, or if the colon is unusually long or large in diameter, the period of normal waiting may be several days, or a week or more. To give purgatives during this time is meddlesome and unjustifiable, except in those cases in which the individual or his relatives become sick with anxiety over the dangers of autointoxication, or in those cases in which headaches actually develop.

It is questionable whether purgatives or laxatives that produce copious movements should ever be given oftener than two or three times a week. Certainly, any one who has been purged and who wishes to get back to normal must expect to wait a day or two for his first normal movement.

Magnesium Sulphate

Danger from Magnesium Sulphate in Conditions of Dehydration. Frank P. Underhill and Robert Kapsinow[9] studied the influence of saline purgatives in a condition of water deprivation on dogs maintained without food and water during seven to nine days. These animals were then given, by stomach tube, doses of either potassium and sodium tartrate, sodium sulphate, or magnesium sulphate. Control experiments were made on fasting animals, water being allowed after the establishment of a condition of concentrated blood. The introduction of either potassium and sodium tartrate, sodium sulphate, or magnesium sul-

(9) Jour. Amer. Med. Ass'n., Jan. 5, 1924.

phate has little or no influence in augmenting blood concentration. In fact, in some instances, there is exhibited a tendency toward blood dilution. In no case did any of the saline administered produce purgation.

The administration of magnesium sulphate to an animal with concentrated blood produces very striking effects. In a few minutes the animal becomes too weak to stand. In a period of twenty minutes there are spastic movements of the feet; respiration becomes at first irregular and rapid; later regular but slow; and a complete anesthesia develops, which is maintained for a period of two and one-half hours. In certain instances the administration of magnesium sulphate under these circumstances caused death from medullary depression.

That the initial condition of concentrated blood is responsible for this unusual effect of magnesium sulphate may be inferred from the results of observations on control animals in which fluid was allowed, although food was withheld.

The present experimental results tend to indicate that, with a significantly increased blood concentration induced by water deprivation, no fluid is withdrawn from the blood by the saline purgatives but, on the contrary, that salt, and possibly the fluid, are absorbed into the blood. The dose of potassium and sodium tartrate or sodium sulphate, administered when absorbed, provoked no recognizable symptoms in the animal. With the administration of magnesium sulphate, however, the symptoms produced were identical with those observed when this salt is given subcutaneously or intravenously.

The results of the present experiments emphasize that *caution should be employed in the administration of magnesium sulphate in conditions in which there exists a possibility of concentration of the blood.*

Hypophysis

Hypophysis in Postoperative Ileus. A. Mayer[1] saw good results from an intravenous injection of 4 to 6 c.c. of solution of hypophysis in 500 to 1,000 c.c. sodium chlorid solution. If evacuation does not set in within 15 minutes, 2 c.c. more of hypophysis solution may be administered.

Physostigmin

Physostigmin and Hypophysis in Postoperative Ileus. Experiments on the isolated human appendix having shown that physostigmin and pituitrin in combination have a more powerful effect in stimulating movements of the intestine than either of these singly, D. S. T. Kerr Cross[2] used this combination successfully in a number of cases of severe postoperative atony, usually obtaining evacuation within ten to twenty minutes, when physostigmin or pituitrin alone failed to do so. Indeed, so far, no case thus treated has failed unless where there was unsuspected mechanical obstruction.

The physistigmin was used in 0.6 mgm. tablets, and as it is a rather slowly soluble drug, the tablet was usually dissolved in 5 minims of warm water and drawn into the syringe. The needle was then thrust into the pituitrin ampule and 0.5 c.c. of its contents also drawn in, and the combined solution injected subcutaneously.

Importance of the Adrenal Glands in the Action of Physostigmin. Charles W. Edmunds and Putnam C. Lloyd[3] find that the leukocytosis, which follows the injection of physostigmin, is due to the epinephrin which is present in increased amounts in the blood owing to stimulation of the adrenal glands by the physostigmin. The leukocytosis is absent if the adre-

(1) Münch. Med. Wochenschr., July 11, 1924.
(2) British Med. Jour., Jan. 5, 1924.
(3) Jour. Lab. and Clin. Med., Oct., 1923.

nals are removed before the physostigmin is given. It is, therefore, an epinphrin effect, and is not due to physostigmin itself. It is entirely analogous to the leukocytosis following the injection of strychnin. It is not necessary that the adrenals be removed by surgical means in order to prevent the leukocytosis. Since physostigmin (and strychnin) act upon the spinal cord to stimulate the glands, drugs which break the connection between cord and glands will functionally isolate the glands and thus prevent their stimulation, with resulting leukocytosis. This functional removal of the gland is accomplished by ergotoxin, atropin, and curara.

DIURETICS

Diuretic Action of Mineral Waters. E. Starkenstein[4] having in a previous study arrived at the conclusion that, while a liter of ordinary water was nearly eliminated within four hours, a liter of phyliological salt solution or Ringer's solution was, to a great extent, retained in the body, was led by further studies to the proposition that *the richer in salt the water the greater the quantity retained in the body.* However, a comparison of the diuretic action of various mineral waters led to the result that a second factor besides concentration must be active, and it was found that this factor was the quantity of free carbonic acid, or rather, the hydrogen ion concentration of the water. It was found, that *the greater the hydrogen ion concentration, the greater the proportion of salt solution eliminated.* The observation that fluids taken by mouth are much more diuretic than on parenteral administration might be explained by the stimulation of gastric hydrochloric acid secretion. One may also be tempted to see a

(4) Klin. Wochenschr., July 8, 1924.

connection between the acidosis and the great diuresis of the diabetic. As to the point of attack of the hydrogen ions, it seems safe to exclude a renal action and to assume an extrarenal influence upon the tissues.

Salt and Water Diuresis Diminished During Menstruation. R. Heilig[5] reports a series of cases in which the elimination of 1,000 c.c. of water was greatly—up to 50 per cent.—diminished during the first two days of menstruation. He obtained a similar result with 15 gms. of sodium chlorid.

The author is unable to pronounce upon the cause of this change, but suggests the possibility of a change in the internal secretions.

Novasurol

Novasurol (Merbaphen) a Mercurial and Antisyphilitic. This double salt of sodium oxymercuri-o-chlorphenoxyl-acetate with diethylbarbituric acid (veronal) containing 33.9 per cent. Hg., originally introduced as an antisyphilitic by Zieler (1917), was, after its introduction, found by Poelchen and Lange, as well as by Saxl, to be a diuretic which surpasses other diuretics in reliability and promptness. It is, at times, efficient where others fail. The application may be intramuscular or intravenous; intravenous injections being more efficient, but also more apt to cause poisoning. The main indications for it are cardiac and cardio-renal affections with edema. Contraindications for its use are acute renal diseases where the functional activity of the kidneys is greatly diminished—most especially, glomerulo-nephritis. In enteritis it should be avoided. Prof. Schlayer[6] considers albuminuria and casts not a contraindication when caused by congestive, and not inflammatory conditions.

Its action begins about one hour after administration and lasts from ten to twelve hours. The average

(5) Klin. Wochenschr., June 17, 1924.
(6) Med. Klinik., No. 45, 1922.

amount of urine eliminated is 2 to 3,000 c.c., but cases of 6 to 7,000 c.c., and even 11,500 c.c. (Hassencamp[7]) are reported. The initial dose is 0.75, the maximal dose 1.5 c.c. of the 10 per cent solution, which is supplied on the market in ampules of 1.2 c.c. Injection should not be repeated any oftener than once in four days. To avoid mercurial by-effects, stomatitis, and diarrhea, attention should be given to the teeth, and constipation corrected previously.

W. Nonnenbruch[8] finds that novasurol also acts as a powerful diuretic in the normal, even when the system has been made salt and water poor by salt poor diet; in this latter respect showing itself superior of theophyllin, which does not act under these circumstances. He believes, as a result of his studies upon normal and sick individuals, that novasurol acts chiefly by mobilizing water and sodium chlorid; but he is unable to demonstrate it by blood examination, as this does not show the enormous changes that must go on to lead to such great effect. P. Saxl and R. Heilig[9] consider the action not due to mercury but to the whole molecule. Its diuretic action can be suppressed by atropin.

J. Flesch[1] suggests, in cases where diuresis is very urgent, to inject novasurol intramuscularly besides the intravenous administration of strophantin. E. Hassencamp[2] reports good results from a combination of novasurol with digitalis.

O. Burwinkel[3] advises that it should be administered in the morning so as not to disturb the patient's sleep by the great frequency of urination. Rest in bed and milk diet should accompany its administration. He believes that, in the future, calomel will be displaced as a diuretic by the much more powerful and energetic

(7) Zentralbl f. inn. Med., Feb. 11, 1922.
(8) Münch. Med. Wochenschr., Oct. 7, 1921.
(9) Wien. Klin. Wochenschr., Oct. 21, 1920.
(1) Ibid., No. 44, 1922.
(2) Zentralbl. f. inn. Med., No. 6, 1922.
(3) Münch. Med. Wochenschr., Feb. 10, 1922.

novasurol. But, like calomel, it also is a two-edged sword. It impresses the patient greatly when, just as predicted by the doctor, liters of urine are passed and dropsical swelling diminishes.

As an *antisyphilitic*, novasurol is claimed to be efficient, but at present is generally used in combination with arsphenamin. G. Villy and H. Schmitt[4] and others report that the mixed administration has the same effect as the giving of the drugs separately but with less by-effect. W. Schmaltz[5] noted a more rapid disappearance of the clinical symptoms than with arsphenamin alone. The combined method, recommended by Prof. Bruck, is generally applied, and is as follows: Into the syringe containing neoarsphenamin, one takes novasurol from the ampule and mixes by shaking. The initial dose is 0.45 gm. (for women 0.30 gm.) arsphenamin and 1 c.c. novasurol solution; the second injection increased to 0.6 gm. (for women 0.45 gm.) arsphenamin and from 1 to 2 c.c. novasurol. Ten to twelve injections are given in one course, and after six weeks' interval repeated.

St. Engel[6] reports good results with novasurol in *congenital syphilis.* The newborn stands both mercury and arsphenamin well, and has, in proportion, a greater tolerance of these drugs than the adult. But the spirocheticidal effect of arsphenamin may result in ill-effects. For this reason he first uses mercury. Quick action is the most important demand. He considers novasurol superior to other preparations in this respect. Skin eruptions commence to disappear after 24 to 48 hours and no trace is found after a few days. Novasurol is too quickly eliminated to have a lasting effect. But in the newborn, where quick action often means saving the life, the lasting effect has not to be considered first. His method is the following: The initial dose of 0.25

(4) Münch. Med. Wochenschr., No. 15, 1922.
(5) Deutsche. Med. Wochenschr., No. 35, 1923.
(6) Klin. Wochenschr., Oct. 15, 1923.

c.c. novasurol solution is injected intramuscularly; then once every 3 to 4 days further injections of 0.5 c.c. are given. Clinical symptoms disappear very quickly. Wassermann is generally negative after three to four weeks. As an after treatment he gives yellow mercurous iodid in doses of 0.005 twice a day. That ends the first course of treatment. When the child is 5 to 7 months old, 6 to 8 injections of arsphenamin are given intravenously in intervals of one week, the initial dose being 0.075, the following 0.15. He considers neo-arsphenamin best suited for this age.

Selian Neuhof[7] finds novasurol a most powerful, indeed, at times, an astounding diuretic. *Its main use seems to be in cases of advanced cardionephritis with edema*—that is, is those with myocarditis, cardiosclerоses, and coronary disease, alone or in combination, with more or less marked edema of the legs and thighs, general anasarca, a secondary hydrothorax, ascites, secondary bronchitis with mucous râles, secondary pulmonary congestion and pulmonary edema, engorged and swollen liver. In other words, it finds its chief indication in edema with general succulence and engorgement of the tissues, serous cavities, and organs—liver, lungs, bronchi, brain, etc. It has been found especially useful, at times, in fact, life-saving, when the usual well-known methods of therapeusis—thorough digitalization and diuretics over long or short periods—have utterly failed. The action of novasurol usually becomes evident within 24 hours after the injection. There is often a tremendous increase in urinary output, edema becomes less, the liver less engorged, pulmonary and bronchial congestion becomes less marked, dyspnea decreases, the patients breathe more comfortably, semistupor from cerebral edema diminishes. The frequency of its administration depends upon the type of case. When edema is massive and the patient cyanotic, injections may be given daily

(7) Therap. Gaz., Jan. 15, 1924.

for two or three days, for the drug is quickly excreted and its maximum diuretic effect usually passes off in 24 hours. When the edema is moderate and the indication is not so urgent, the injections may be given every two or three days. Usually three injections are sufficient, even in severe cases.

Novasurol has but a very slight effect in non-edematous patients. It has no effect in the absorption of inflammatory exudates, such as pleurisy with effusion.

There are two contraindications to the use of novasurol—acute (not secondary) glomerulonephritis, and enteritis. There are two effects against which the patients should be warned and the physician prepared. Novasurol occasionally produces severe stomatitis and gingivitis and an annoying colic, alone or with diarrhea. It is therefore necessary to have patients take good care of their teeth and gums during the period of the drug administration. For the colic and diarrhea, as well as for the stomatitis, ordinary remedies are sufficient. During the time of novasurol treatment, and for a few days thereafter, food is preferably limited to the Karrel diet with a daily intake of 1,000 c.c.

ANTISPASMODICS

Atropin Series

Antispasmodic Inhalation for Bronchial Asthma. E. Edens[8] publishes the following prescription which, though by no means new, has given such excellent results at his hands during the last fifteen years that, he believes, it should be more generally known.

℞

Atropin sulphate	0.03-0.05
Cocain hydrochlorid and Potass. sulphate, of each	0.3-0.5
Glycerin	3.0
Solution epinephrin hydrochlor. (1:1000) to make	25.0

(8) Klin. Wochenschr., July 22, 1924.

If the muscosa is very sensitive, he sometimes eliminates potassium sulphate and uses only 15 c.c. of epenephrin solution and enough physiologic salt solution to make 25 c.c.

This is best administered by an inhaler driven from an oxygen tank, though other inhalers might be used less successfully. The author has the patient inhale deeply with open mouth for one minute, then rest for three to five minutes so as to give the remedy a chance to act and an opportunity to penetrate deeper into the bronchi at the next inhalation. Generally three to four inhalations of one minute each suffice to make respiration free and easy. During the inhalation the eyes should be closed so as to prevent any of the material entering the conjunctiva. After the inhalation the mouth should be rinsed with physiologic salt solution.

The inhalations may be repeated as often as desired, as the amount absorbed in view of the fine degree of subdivision is exceedingly small. Hence, it is permissible to use the inhalation even at the beginning of mild attacks; and it seems that such aborting of each attack has a favorable influence upon their repetition.

In very severe attacks Edens uses, in addition to inhalation, the following subcutaneous injection:

Morph. hydrochlorid	0.01
Atropin sulphate	0.0005
Sol. Epinephrin hydrochlor (1:1000)	1.00

Effect of Atropin Upon the Stomach. T. Barsony and L. v. Friedrich[9] report that large doses of atropin lead to depression of the muscles of the stomach, decreasing the peristaltic tonus and slowing evacuation, while small doses of atropin have only a very brief effect, if any. The depression was greater in patients suffering from gastric ulcer than in normal people. The changes are conveyed by means of the Auerbach plexus and not by the vagus. In the presence of cholin, atropin paralyzes the muscles; in its absence it excites them.

(9) Deutsche. Archiv. f. klin. Med., October, 1924.

The contradictory reports of Otvos and Lasch (abstr. in Pract. Med. Series, Vol. VI, 1922, p. 143) are due to a different technique and dosage. If the authors injected 1 mgm. atropin subcutaneously, they obtained the same result as Otvos (pyloric spasm) while the result of an intravenous administration of 1 mgm. atropin agreed with the report of Lasch, who obtained a lessening of peristalsis and a relaxation of the antrum pylori. Hence both are right.

As to secretion, an intravenous injection of ¼ mgm. of atropin was not effective, while 1 mgm., injected intravenously, acted very noticeably upon the acidity, often reducing it to zero. Fractional determination upon the empty stomach gave the best results. No change in the secretion was generally noted after subcutaneous injections. Sometimes the acidity was slightly reduced.

The Variable Action of Atropin on the Intestine Explained. K. Schübel[1] believes that the presence of varying amounts of cholin in the intestine is responsible for the diversity of results obtained with atropin upon the bowel. Cholin, which has been called the hormone of intestinal peristalsis, is a substance that belongs pharmacodynamically to the pilocarpin group. It stimulates Auerbach's plexus. In an intestine thus stimulated by cholin, the minutest dose of atropin suffices to inhibit the peristalsis. If the intestine contains but little cholin, atropin produces excitation; if it contains much cholin, inhibition predominates.

Mydriatics and Cycloplegics. G. Henry Mundt[2] summarizes his experiences in refraction cases as follows:

Atropin sulphate is probably the most reliable and safest drug. Hyoscin hydrobromid is practically as certain and, if it were not for the general attitude on the subject, he would probably use it in place of atropin sulphate. There is a great advantage here in that the pupil does not remain dilated so long and action is

(1) Klin. Wochenschr., Apr. 15, 1924.
(2) Illinois Med. Jour., December, 1923.

quicker. Homatropin hydrobromid is practically satisfactory beyond the age of 45, and in probably 75 per cent. of cases from 15 to 45 years.

In treatment hyoscin hydrobromid has a very wide field of usefulness. It is superior to atropin sulphate, even in solid form, where difficulty is experienced in dilating the pupils.

On the method of administering these remedies Mundt says he has abandoned the use of discs. He uses a fresh solution (made fresh at least once a week) of 2 per cent. homatropin hydrobromid and 1 per cent cocain hydrochlorid. This is dropped in the conjunctival sac every five to ten minutes a varying number of times, dependent upon the age of the patient—from fifteen to twenty years eight times, 20 to 30 six times, 30 to 40 four times, 40 to 50 three times, and beyond 50 once or twice only.

Atropin: for refraction, aqueous solution is used four times a day for three or four days—in patients beyond six years of age a 1 per cent. solution, three to six years ½ per cent., and weaker below three. In treatment, if the aqueous solution of 1 to 2 per cent. atropin can be flooded over the cornea when there has been a few drops of 4 per cent. cocain hydrochlorid previously used, he thinks the action is superior to the ointment. He has never been able to convince himself that the ointment was more valuable than aqueous solution if the solution was used as above indicated.

Hyoscin: the hydrobromid is used in a solution; the maximum dose in adults being 2 small drops of ½ per cent. solution, with the excess mopped up at once, and the pressure made over the sac. This means that one drop may be used in each eye, or 2 drops, with an interval, in one eye. The above is the maximum dose and must be used with great caution. He more frequently uses a ¼ per cent. solution as above, but in iritis the ½ per cent. solution is much more active. The

¼ per cent. solution may be used twice, with care, in patients as young as twelve years; while from twelve to eight about 1/6 or 1/8 per cent., and from eight down a much weaker solution, must be used.

Atropin Dosage in Children. In treatment of congenital stenosis of the pylorus A. Johannessen[3] gives at first 1 and then 2 drops of the 1:1,000 solution of atropin sulphate four or five times a day, half an hour before feeding. The action of the drug is manifest in a few days, but its full effect does not appear until the tenth to the fourteenth day. The drug must be continued for nine or ten weeks. The largest daily dose was 0.7 mgm.; the usual dose was 10 drops, fractioned. Atropin may be used in about the same doses in whooping-cough and the exudative diathesis. Signs of intolerance are nothing more serious than occasional briefly transient redness of the face and dilatation of the pupils.

Pilocarpin

Pilocarpin in Urinary Retention. A. Cain and P. Oury[4] found pilocarpin very efficient in cases of spasmodic retention of urine, especially in the course of nervous diseases. Pilocarpin acts by way of the vegetative nervous system. Micturition sets in regularly from eight to ten minutes after injection, together with profuse sweating and salivation. The latter often last longer than the first. The quantity of urine eliminated varied between 400 and 1,500 c.c. The author used pilocarpin hydrochlorid in doses of 0.01 gm. injected hypodermically. This dose may be repeated once in the 24 hours.

Benzyl Benzoate

Benzyl Benzoate in Angina Pectoris. Robert H. Babcock[5] has prescribed the remedy, in approximately

(3) Ugeskrift for Læger, Feb. 7, 1924.
(4) Presse Méd., Oct. 27, 1923.
(5) Jour. Am. Med. Ass'n., Jan. 19, 1924.

twenty instances, of what seemed typical attacks of angina pectoris. Of these, six at least, have been so distinctly relieved as to justify daily employment of the remedy for months, or so long as benefit is experienced. In some cases, very slight, if any, amelioration of pain has resulted. In instances of hypertension, no invariable or sustained reduction of blood pressure has been observed.

In no instance have harmful effects been detected. Administered in milk or cream, it does not appear to disturb the stomach. As a general rule, 30 drops, poured directly from the bottle, are ordered four times daily. The remedy would appear to prove efficacious in cases in which vascular tension or spasm produces such a degree of intra-aortic pressure as to pinch the sensory nerve endings richly supplied to the aortic coats.

Benzyl Benzoate Does Not Lower Blood Pressure. C. M. Gruber and H. H. Shackleford[6] find that benzyl benzoate taken in 25 or 30 drop doses (20 per cent. in alcoholic solution) has no immediate depressant effect on blood pressure. Doses of 30 drops, four times a day, taken for four to eighteen days, had no effect on the blood pressure in cases of hypertension.

Effect of Benzyl Given by Mouth. Charles M. Gruber[7] could not detect any change in blood pressure in dogs when benzyl alcohol, benzyl acetate or benzyl benzoate was administered orally. This result differs from the results of previous workers who administered the drugs subcutaneously, intramuscularly, intraperitoneally or intravenously in the same experimental animal. On the other hand, the drugs of the nitrite series lower both systolic and diastolic blood pressures in normal, unanesthetized dogs when given by mouth, the same as when given clinically in human beings. Moderate doses of benzyl benzoate, 20 per cent. by volume,

(6) Jour. Lab. and Clin. Med., July, 1924.
(7) Ibid., October, 1923.

in alcohol, produces a fall in blood pressure. This fall is due, the author believes, to the alcohol they contain, and not due to the benzyl esters; for in susceptible, unanesthetized animals, moderate doses of ethyl alcohol produce a fall in blood pressure.

When given orally benzyl alcohol, benzyl acetate, and benzyl benzoate do not alter the pulse rate. The drugs of the nitrite series and ethyl alcohol cause acceleration of the pulse due to the fall in blood pressure and resultant anemia of the cardiac centers.

Benzyl alcohol and benzyl acetate possess emetic actions. This is also observed in some animals with benzyl benzoate. The action is due to local irritation of the alimentary canal and not to excitation of the vomiting center.

Moderate doses of benzyl alcohol, benzyl acetate, and benzyl benzoate possess cathartic actions. This, however, is much more marked and of more drastic character with the two former substances in which profuse watery stools result. This action is due to the local irritation by the drug, since (1) the time interval in most cases is too brief to be due to relaxation of the intestine, and (2) since subcutaneous and intramuscular injections are not accompanied by evacuation of the bowels.

Camphor

An Antispasmodic for the Bile Passages. K. Westphal[8] recommends a solution of camphor, 2 gm. in oil of peppermint 8 c.c., to relieve spasm of the bile passages. By means of duodenal intubation, it has been found that ½ to 1 c.c. of this preparation caused a delay in the appearance of the pepton reflex up to 30 minutes, which was followed by increased secretion of the bile. Clinically, it was found that 25 to 30 drops of this preparation, taken on sugar, generally produced a prompt relief of

(8) Klin. Wochenschr., June 17, 1924.

moderately severe pains, lasting, however, only one to two hours. In very severe attacks in which this remedy fails, atropin in doses of 0.5 to 1 mgm. is required.

Camphor-in-Oil of No Value as Cardiac Stimulant. H. M. Marvin and J. D. Soifer[9] report a study of fourteen patients with heart failure, and two normal persons, who received camphor intramuscularly in repeated small doses and single large doses, the total amount varying between 0.6 gm. and 3 gm. In none of the patients did the camphor exert any demonstrable action whatever on the heart rate, respiration, blood pressure, vital capacity, electrocardiogram, or general clinical condition of the patient. The subsequent administration of digitalis resulted, in ten of twelve patients, in prompt and definite improvement. Hence, camphor has no demonstrable action on the circulation in congestive heart failure, and therefore no rational place in the treatment of that condition.

Ether

Treatment of Pertussis With Ether. Cleon C. Mason[1] reports 26 cases of pertussis treated by the deep intramuscular injection of ether as described by Genoese (1922). The ether injections are made with a long, fine, platinum needle, deep into the buttocks. The dosages used were: First day, 0.5 c.c., two injections; second day, 1 c.c., two injections; third day, 1.5 c.c., two injections; fourth day, 2 c.c., two injections; fifth day, 2 c.c., one injection; each day thereafter, the same amount as on the fifth day. These dosages were slightly reduced for children under one year. The injections did not seem especially painful. In only one instance was there any local reaction. Sixty per cent. of the patients stopped coughing and were apparently cured; 24 per cent. were definitely benefited; 16 per cent. failed to respond or

(9) Jour. Amer. Med. Ass'n., July 12, 1924.
(1) Ibid., Dec. 22, 1923.

became definitely worse. The earlier the treatment is instituted, the greater the possibility of good results. Four additional cases were treated by the high rectal injections of 6 c.c. of a 40 per cent. ether solution in olive oil, repeated every six hours. Two patients stopped coughing quite promptly; and two failed to respond.

Nitrites

Nitroglycerin in Tinnitus Aurium With High Blood Pressure. Wharry[2] finds nitroglycerin of great value as a therapeutic agent in the cases of tinnitus aurium associated with a high blood pressure. In such cases it appears to have a specific effect in relieving the tinnitus.

GENERAL ANESTHESIA

Ethylene

Blood Reaction in Ethylene and Nitrous Oxid Anesthesia. Chauncey D. Leake and Alrick B. Hertzman,[3] as a result of experimental work on large dogs, conclude that neither ethylene nor nitrous oxid, when used as anesthetic agents with oxygen, influence the blood reaction so markedly or so rapidly as does ether or chloroform, though it is impossible to maintain anesthesia under nitrous oxid and oxygen without some anoxemia. The effects of ethylene-oxygen anesthesia on the blood reaction seem to be related to the dgree of anoxemia present. If there is no anoxemia, the Ph and carbon dioxid content of arterial blood tend to fall slightly, but not beyond normal limits, with half an hour's anesthesia. If anoxemia is present, there is an initial increase in the arterial Ph, with inconstant changes in the carbon dioxid content. This alkalotic tendency may persist from fifteen to thirty minutes,

(2) Lancet, May 3, 1924.
(3) Jour. Amer. Med. Ass'n., Apr. 12, 1924.

depending on the degree of anoxemia, and is followed by a fall in both the Ph and the carbon dioxid content.

Metabolism Study of Ethylene Anesthesia. H. A. Oberhelman and Hattie A. Dyniewicz[4] arrive at a very favorable opinion regarding ethylene-oxygen anesthesia. The increase in blood sugar and decrease in alkali reserve were found less with ethylene-oxygen anesthesia than with ether, chloroform, or nitrous oxid. At no time did the change in blood sugar and alkali reserve approach a dangerous level. The changes in blood pressure produced by ethylene-oxygen anesthesia are much more like those of normal sleep than are those which occur with the anesthesia brought about by ether, chloroform, or nitrous oxid.

Ethylene Anesthesia. Arno B. Luckhardt and Herman L. Kretschmer[5] conclude, on the basis of experience with 125 urologic cases, that ethylene-oxygen anesthesia is the anesthesia of choice for a number of urologic purposes. In cystoscopic examinations, a convenience that is of immeasurable gratification to the urologist is to have at hand an anesthetic which will give good relaxation with a prompt recovery, especially when repeated examinations are carried out, thereby avoiding repeated ether narcosis with its unpleasant sequelae. All these desirable points are inherent in ethylene. Ethylene is much more desirable than nitrous oxide-oxygen because of the more perfect relaxation under ethylene-oxygen anesthesia. Also, when fulguration was used, ethylene has yielded gratifying results. The patients were quickly anesthetized, the anesthesia left nothing to be desired, recovery was prompt, and untoward after-effects were absent.

They have likewise found ethylene of particular value in the treatment of carcinoma of the prostate with radium-bearing spears inserted into the prostate by passing the needles directly through the perineum, without

(4) Jour. Amer. Med. Ass'n., Dec. 20, 1924.
(5) Jour. Urol., April, 1924.

pain. This procedure can be accomplished much more quickly under ethylene than when sacral anesthesia is resorted to.

Ethylene is especially of value in both major and minor surgical procedures in "bad risk cases," as in the surgical treatment of elderly patients suffering from enlargement of the prostate, or carcinoma of the bladder.

Because of the non-irritating properties of ethylene on the pulmonary tissues and the bronchial mucous membrane it can be used where ether is counterindicated. Since ethylene has no demonstrable effect on the heart muscle directly, and only a slightly stimulating effect, if any, on the cardio-inhibitory center, there is no known counterindication to its use in cases with valvular lesions and myocarditis. The apparent absence of significant blood-pressure changes, even during deep ethylene anesthesia, indicates its safety in cases of hypertension and arteriosclerosis. Nitrous-oxide is more likely to cause an increase in blood pressure, when it is pushed to obtain a greater relaxation, because of an asphyxial rise. The cyanosis often seen in nitrous-oxide anesthesia means asphyxia of all tissue, including the kidney. Asphyxia of the kidney, where the functional reserve is greatly diminished for one or another reason, particularly in the type of case under discussion, is certainly to be avoided if possible. Ethylene has a less toxic effect on the kidney parenchyma than has ether, and because the patients never get cyanotic, it is better than nitrous-oxide. Asphyxia of even normal kidneys for short periods of time leads to more or less disturbance of kidney function, which, of course, should be avoided, if possible, in all cases suffering from the effects of back pressure, cardiac decompensation, and infection. So far, no counterindications to the use of ethylene-oxygen anesthesia have been found in genito-urinary work.

Since ethylene forms with air and oxygen, in proper proportions, an inflammable or even explosive mixture, free flames, electric cauteries, electric gas warmers, and

sources of electric sparks should be excluded from the room. In the author's work, the machine used for fulguration has been placed at some distance from the patient and the field of operation. The electrodes have been led through holes drilled through the walls of the cover, which forms an almost air-tight joint with the apparatus delivering the powerful induction sparks. It seems highly unlikely that an explosive mixture of the gas can, under these conditions, ever get under the lid and replace the air confined in the machine.

Explosiveness of Ethylene Mixtures Need Not Be Especially Feared. In view of a widespread fear that there existed a great danger of ethylene exploding, a number of experiments were performed by W. Easson Brown[6] who finds that pure ethylene, without the addition of air or oxygen, cannot explode; nor can the ethylene-oxygen mixture delivered to the patient, which, in practice, varies from 10 to 25 per cent. of oxygen, the remainder being ethylene. The mixture that would explode contained a minimum of from 40 to 45 per cent. of oxygen. Any mixture having a higher per cent. of oxygen explodes with violence increasing directly with the oxygen percentage; the maximum violence being reached with three volumes of oxygen to one of ethylene. Though mixtures containing a higher amount than 25 per cent. of oxygen might conceivably be used for short times, either when the anesthesia became too deep, or as the patient recovered, there should be no reason for fearing this agent any more than nitrous oxid-oxygen, or even pure nitrous oxid passing through an ether chamber, which forms a violently explosive mixture. Another possibility of an ethylene mixture is that the expired ethylene coming out of the spill valve in the mask, might, in turn, form a mixture with air which would be explosive. Experiments have shown that a mixture of from 5 to 10 per cent. of ethylene in air is explo-

(6) Jour. Amer. Med. Ass'n., Mar. 29, 1924.

sive. As it would require somewhat in excess of six hours' continuous anesthesia to form a mixture of 5 per cent., which is the minimum explosive mixture, and this without the slightest room ventilation, there is only a remote possibility of an explosion from this source.

Morphin Scopolamin

Morphin Scopolamin Anesthesia. Eugene R. Lewis[7] has, during the last fifteen years, used scopolamin—morphin anesthesia in operating on poor surgical risk cases, and his unbroken series of successes in these cases led him to apply this hypodermic anesthesia to "good risk" patients as well. For the last fourteen years he has used scopolamin morphin injection as the anesthetic method of choice in ear, nose, and throat surgery. In operative procedures in which there is a definite advantage to the operator, without counterbalancing disadvantage to the patient, in retaining a certain awareness and cooperability on the part of the patient, the author uses hypodermic injections of 8 to 10 mgm. of morphin with 0.6 mgm. of scopolamin, which usually proves very satisfactory. There is another class of operative procedures which offers no advantage to the operator or the patient in retaining this cooperative state of the patient. In such cases he has used, as a routine, from 16 to 20 mgm. of morphin with 1.2 mgm. of scopolamin at one injection, with the intention of producing an adequate degree of general narcosis. This class of cases includes such procedure as tonsillectomy, opening peritonsillar abscesses, tympanomastoid operations, radical mastoidectomy, simple opening of the mastoid, and certain extensive operations on nasal sinuses. Experience has taught the author that young children require morphin in relatively larger doses than adults, and that older adults (over 55 to 60 years) require relatively less morphin than those between the ages of twenty and 60,

(7) Jour. Amer. Med. Ass'n., Oct. 13. 1923.

contrary to textbook teachings. The author aims to use sufficient scopolamin and morphin at one injection to produce, not only complete absence of apprehension, but also, dryness of the mucous membranes, complete general relaxation, sleep, and profound obtunding of the sensorium. This condition supervenes usually from 40 to 60 minutes after the injection; but occasionally as much as 90 minutes may elapse before the required stage is reached. There is no necessity for speed, as the narcosis may be counted on to endure for two or three hours.

From 40 to 60 minutes after the hypodermic injection of morphin and scopolamin, the patient's condition is suitable for the second preoperative step. There is now no difficulty in proceeding with necessary local anesthesia, which is produced with a minimum of topical applications and local injections.

The author has encountered certain disquieting symptoms in relatively rare instances—tremor, tachycardia and palpitation—but never to a degree which interrupted the prosecution of operative work. In very rare instances, excitement and delirium of mild degree are encountered.

LOCAL ANESTHESIA

In General

Local Anesthetics. As the result of an analysis of the reports of 43 deaths submitted to the committee for the study of toxic effects of local anesthetics of the American Medical Association, Emil Mayer[8] its chairman formulates the following recommendations.

Cocain should not be injected into the submucous tissue or subcutaneously.

Cocain paste ("mud") should not be used as a preoperative measure. Its use in that way is unreservedly condemned.

(8) Jour. Amer. Med. Ass'n., Mar. 15, 1924.

Local anesthetic should not be injected into the urethra when trauma or stricture exists.

Especial care should be exercised in the use of local anesthetics when constitutional disease of a grave character exists.

Local anesthetics may be applied safely in the following concentrations and total amounts:

Cocain in the mouth and epipharynx (preoperative), 5 per cent.; in the nose, not over 10 per cent., and in total amounts of from 10 to 15 minims, containing from 1 to 1.5 grains; in the eye, not over 5 per cent.; in the larynx and bronchi, not over 20 per cent.—preferably 10 per cent. in two applications—and not over 15 minims total, containing from 1 to 1.5 grains.

Procain should not be used in greater concentration than 1 per cent.; apothesin not greater than 2 per cent.; and not more than 1.5 grains; butyn should not be injected, but may be applied in 2 per cent. solution.

Epinephrin serves a valuable purpose in causing a bloodless field and in delaying the absorption of the local anesthetics, especially procain; but the addition of epinephrin in amounts of 1 mgm. or more to a solution of cocain often results in a greater degree of toxicity than that from cocain alone, when rapid absorption takes place. Hence, the use of larger doses of epinephrin with cocain is deemed unsafe, and epinephrin should not be used in greater concentration than 1:10,000, and of this, not more than 10 minims with cocain. Somewhat larger total amounts of epinephrin may be used with solutions of procain, but not more than 1 mgm. of epinephrin should be used, and even this dose may be unsafe in patients suffering with hyperthyroidism.

When severe toxic symptoms result, efforts should be made to sustain the heart in order that the drug may be carried to the liver, where it is destroyed. Cardiac massage, and, perhaps, epinephrin in proper intracardiac doses, are indicated when the heart has stopped. The committee cannot endorse the views of those who recom-

mend large intracardiac doses of epinephrin, and not more than 2 c.c. (30 minims) of a solution of 1:10,000 is recommended. The committee is unable to state the dosage of strophanthin and digitalis in such cases, but large doses are almost certainly dangerous. Artificial respiration is indicated, as a rule.

There is no evidence that the inhalation of ether or the injection of morphin has any value as an antidote to the local anesthetics, but, on the contrary, the use of morphin in such cases is considered distinctly dangerous. Ether is possibly of value in controlling convulsions.

All doses of local anesthetics, however applied, should be measured accurately. This is manifestly impossible when preparations of unknown composition or concentration, including those that have deteriorated, are used, and the committee condemns their use as unscientific and dangerous.

Stock solutions of local anesthetics which have been used for numerous injections are seldom sterile, and their routine use is condemned. All solutions should be freshly made and should be sterile. They should be used at about body temperature when injected. Injections should be made slowly, while avoiding lateral pressure, and sufficient time should be allowed to elapse for anesthesia to develop before an operation is started. The surface at the seat of operation should be dried, if necessary, and sterilized by painting with tincture of iodin or with another effective disinfectant.

Owing to the danger of misunderstanding when procain is pronounced indistinctly, and of the substitution of cocain, great care should be taken when procain is ordered verbally. The committee recommends that the proper authorities consider the question of a name for procain that will be free from this disadvantage. The use of sealed ampulses of procain tends to prevent the substitution of cocain for procain. The danger of substitution will be lessened if all solutions of cocain are tinted as follows: add sodium flourescein, 1 mgm. for

each gram of cocain hydrochlorid used. Solutions of procain and other local anesthetics should not be tinted.

Local Anesthetics Compared. A. J. Copeland[9] compared, by experiments on dogs, cats, rabbits, guinea-pigs, and mice, the following local anesthetics: cocain, beta-eucain lactate, alypin, novocain, stovain, holocain, tropacocain, apothesin, phenolain, butyn, and "tutocain." Tutocain is not decomposed by boiling, and has the advantage over butyn that it can be disolved in saline. He concludes that the best of the local anesthetics for the eye are cocain and butyn. Tutocain may also have a use. Tropacocain, novocain, and eucain are less valuable for deep anesthesia. For the nose, cocain and tutocain are alone useful. For subcutaneous injection, novocain is much the best. Besides cocain, it is believed that the properties of butyn and tutocain may render them addiction drugs.

Tissue Damage from Local Anesthetics. H. Rhode,[1] acting on the assumption that the influence on unicellular organisms such as paramecium, erythrocytes, spermatazoa, yeast, and plant embryoes, enables one to arrive at an opinion regarding the effect of poisons upon tissue cells, studied various local anesthetics in this manner. In accordance with these observations, eucain and stovain were found to be powerful cell poisons in very dilute solution, hence might be considered unsuitable for use in man. *The least harmful agents were cocain and procain.* Tropacain and alypin range between these two groups. Saligenin and benzyl alcohol were some what irregular in their effects, but showed sufficiently low toxicity to be considered useful agents.

Influence of Colloids on Local Anesthesia. H. Graf[2] reports that isoviscous animal and vegetable colloids have diametrically opposite effects upon the rapidity of action of procain and cocain solutions. While animal

(9) British Med. Jour., July 12, 1924.
(1) Zeitschr. f. d. ges. exp. Med., 1923.
(2) Schweiger. Med. Wochenschr., No. 22, 1924.

colloids, such as beef serum, shorten the latent period, increase the intensity, and prolong the action, vegetable colloids act just the reverse, diminishing these effects. Lipoid emulsions likewise act unfavorably.

Tutocain

Tutocain a Local Anesthetic, for Surface as Well as Infiltration Anesthesia. Tutocain, the hydrochlorid of p-aminobenzoyl-α-dimethylmino-β-methyl-γ-butanol, comes in fine, needle-shaped crystals, quite soluble in water, non-irritant, and not impaired in their anesthetic efficiency by boiling. W. Schuleman[3] reports that the toxicity is about the same as that of procain, hence much less than that of cocain. Inasmuch as the anesthetic efficiency of tutocain is four times that of procain, it is claimed to be much safer than the latter, having a higher anesthetic value. The slight dilatation of the blood vessels produced by tutocain, is readily antagonized by the addition of epinephrin.

G. Düttman[4] in experiments on himself and others, showed that infiltration of a 0.1 to 0.2 per cent. solution of tutocain produced complete anesthesia immediately; no irritation and no ill effects being observed. He used tutocain in infiltration and regional anesthesia in about 200 cases, and recommends a ⅛ per cent. solution, with addition of epinephrin, for infiltration anesthesia, and ¼ per cent. solution for regional anesthesia. In five of the cases a slight transient albuminaria was noted. Some cases showed a transient lowering of blood pressure and of pulse rate. For *lumbar anesthesia,* 1 to 3 c.c. of a 1 per cent. solution of tutocain was successfully used in 25 cases. The instillation of 45 mgm. produced an anesthesia lasting from ¾ to 2 hours. Paralysis and paresthesia were not noted. The author found that tutocain had a strikingly slight effect on the motor nerve roots.

(3) Klin. Wochenschr., Apr. 15, 1924.
(4) Ibid., July 29, 1924.

The patients were capable of moving their toes and feet to some extent throughout the anesthesia period. In his opinion, the danger of paralysis of the respiratory center is less with tutocain than with the anesthetics most commonly used for this purpose.

Prof. Braun[5] reports satisfactory results with tutocain as a *local anesthetic* in about 750 cases. He used a solution four times weaker than that of procain commonly used for the same effect. In infiltration and regional anesthesia, as well as in splanchnic and parasacral anesthesia, ⅛ per cent. solution of tutocain has the same efficiency as a ½ per cent. solution of procain. Occasionally as much as 200 to 300 c.c. of the ⅛ per cent. solution was used. The quantity of epinephrin added was the same as that commonly employed with procain. Solution of tutocain alone does not undergo change readily; whereas, of course, solutions of tutocain with epinephrin have to be freshly made for each operation. Freese reports that solutions of tutocain can be kept for two or three months without losing their anesthetizing power.

K. Gentzsch[6] reports 50 cases of tutocain surface anesthesia in *rhino-laryngology,* and concludes that tutocain is an efficient anesthetic in intranasal operations, but not to be recommended in laryngeal operations. Its anesthetizing efficiency can be increased by the addition of phenol.

In ophthalmology, H. Freese[7] reports subconjunctival or subcutaneous instillation of 0.5 per cent. (0.6 c.c.) and 0.75 per cent.. (0.4 c.c.) were non-irritant, complete anesthesia lasting up to 40 minutes. Patients did not complain about ill effect. A slight hyperemia of the conjunctiva and the pericorneal blood vessels was observed which could be readily antagonized by adding epinephrin. Dilatation of the pupils set in considerably later

(5) Klin. Wochenschr., Apr. 22, 1924.
(6) Ibid., July 8, 1924.
(7) Ibid., Aug. 19, 1924.

than the anesthesia, making measurement of tension possible. Addition of 1 to 2 drops of eserin prevented the dilatation of the pupils. Instillation, every three minutes, of 1 to 2 drops of a 2 per cent. solution of tutocain during 45 minutes did not impair the epithelium of the cornea. Solutions of 1 to 5 per cent. were used in operations. A 3 per cent. solution of tutocain acts as strongly as a 2 per cent. solution of cocain. He concludes with the statement that tutocain is superior to all other anesthetics because: (1) it takes the place of the three anesthetics commonly used, (2) it does not injure the epithelium, (3) it shows less toxicity on absorption, (4) it does not produce any unpleasant sensations, (5) it is less expensive than cocain, holocain, or procain. To this may be added that it may be boiled for a short time without decomposition. Its only disadvantage, as compared with cocain, is that it does not constrict the blood vessels. But when this is desirable, the effect may be obtained by the addition of a little epinephrin.

Quinin Series

Quinin and Urea Injection in Acute Lumbago. H. S. Souttar[8] reports instantaneous and permanent cures in a number of cases from the injection of quinin and urea hydrochlorid in 1 per cent. solution, 5 c.c. being injected through a long fine needle into the centre of the tender spot. Within ten minutes the acute pain disappears and the patient can move freely. A sense of stiffness remains, and a curious feature is that the patient may complain of a general malaise. The author has little doubt that the treatment would be equally effective in those similar cases of torticollis and pleurodynia where a localized tender spot is a marked feature.

Quinin and Urea Hydrochlorid in Pruritus. M. P. Moorer[9] infiltrates the itching area, be it arms, vulva

(8) British Med. Jour., Nov. 17, 1923.
(9) Jour. Amer. Med. Ass'n., Sep. 6, 1924.

or scrotum, with 0.5 per cent. quinin and urea hydrochlorid solution. By this, itching is at once arrested; excoriations rapidly heal; and within a few days the skin resumes its normal smoothness and luster. Anesthesia persists for from several days to as many weeks; and, at the expiration of this period, a second, and sometimes third infiltration is or may be required. It has not been necessary to employ a fourth infiltration in any case thus far treated, as the causative factor is searched for; and, if found, eliminated during the days of freedom from itching produced by this simple measure. Thus skin tabs should be removed or other operative rectal procedure carried on to insure permanent relief.

The technic consists in rendering the part clean with water, a good soap, and a soft sponge; application of a solution of mercurochrome-220 soluble as an antiseptic, and the injection of a small area with 1 per cent. procain as a starter. The remainder of the diseased skin is then infiltrated, after which the underlying subcutaneous structure is ballooned out with quinin and urea hydrochlorid solution until the patient complains, on resuming a chair, that he is "sitting on a cushion."

The precautions to be observed follow. It is wise to administer hypodermically 0.015 gm. of morphin before beginning this treatment, for the prevention of shock. Not more than 10 c.c. of 1 per cent. procain should be used, but quinin and urea hydrochlorid solution from 0.25 to 0.5 per cent. strength may be used in any necessary quantity, as much as 200 or 300 c.c. (quinin and urea hydrochlorid solution in greater than 0.5 strength may produce a slough or an unpleasant induration). The pressure on the terminal nerves produced by the forcible injection of fluid in large amount brings about a temporary paralysis equal in duration to that produced by severance of their fiaments with a knife, and to the mind of the average patient, much more acceptable.

Optochin in Hay-Fever. Haike[1] reports good results from drops applied to the conjunctive and painting of the nasal mucosa with following solution.

℞

Optochin hydrochlorid	0.25
Glycerin	2.00
Distilled water, to make	25.00

This solution is also useful prophylactically applied two to three times a week. It should be freshly prepared as it becomes inactive within a week.

Regional Anesthesia

Regional Anesthesia should be more generally employed, is the plea made by M. E. Bland[2]. There are two methods of inducing regional anesthesia—field block and nerve block. In field block, the anesthesic solution is injected in such a manner as to surround, by the solution, the operative field and the nerves as they approach the region of operation. In nerve block, the anesthetic solution is injected either directly into the nerve or into its immediate vicinity, thereby interrupting the conductivity. Intraneural injection, however, is never used to produce surgical anesthesia, as the same result can be obtained by an extraneural or paraneural injection without injury to the nerve. If the injection is made at the point at which the nerves leave the spinal canal, it is called paravertebral block, the terminology always being in accordance with the location of the injection. The author finds that it is not necessary to execute a typical paravertebral injection, that is, to bring the point of the needle in direct contact with the transverse process and to bathe the nerves in anesthetic fluid at their point of exit from the vertebral canal. A simple infiltration of the tissues lying under the deep fascia at the posterior border of

(1) Deutsche. Med. Wochenschr., v. 49, No. 22, 1923.
(2) Jour. Amer. Med. Ass'n., Aug. 9, 1924.

the sternocleidomastoid (in cervical paravertebral anesthesia) will give ample anesthesia. This injection can be made from one point situated at the posterior margin of the sternomastoid, on a level with the lower angle of the jaw. The anesthetic is completed with a subcutaneous injection circumventing the operative field. This technic is much less difficult of execution. Especially is this true in fat persons in whom it is frequently impossible to palpate the cervical transverse process, making it exceedingly difficult to find the tip of these bony prominences with the point of a needle.

In the upper abdomen, for anesthesia of the stomach, gallbladder, or transverse colon, the author employs splanchnic anesthesia, according to the anterior method of Braun. The one outstanding objection to the anterior method is the fact that the hand of the operating surgeon must be placed within the abdomen before the abdominal contents are anesthetized. Even this objection can be greatly negated by a little practice and dexterity.

The chief danger in the use of procain is from injecting procain solution within the lumen of a blood vessel. While procain, when properly used, is practically nontoxic, when injected into the circulation, it becomes extremely toxic and may cause sudden death. If just two points are remembered, the accident of injecting procain into the vascular stream will never happen, *i. e.*, (1) whenever possible, one should keep the needle in continuous motion while injecting; and (2) if it is necessary to inject with the needle in a stationary position, as in the case of an anterior splanchnic anesthesia, one should aspirate for blood before each syringeful is injected. These two points cannot be emphasized too strongly, as, in the author's opinion, all procain deaths are due to the presence of procain in the blood stream. By observing these two points with the utmost care, the author has, up to the present time, not seen a single case

of procain poisoning, in spite of the fact that he has used as much as 250 c.c. of 0.5 per cent. procain solution at a single operation.

Paravertebral Anesthesia. O. S. Lowsley and W. S. Pugh[3] have found paravertebral anesthesia quite satisfactory in a series of approximately 100 renal operations.

"The confidence of the patient is as absolutely essential here as it is in all regional procedures. Naturally, more difficulty will be experienced in highly nervous persons than in those of a more stolid type. The patient must be apprised of the fact that he will feel a half dozen or so little needle pricks when the first injections are made. After these, perhaps a few pulling sensations may be felt, which will at once be relieved on his calling attention to them.

"An opium suppository of 0.065 gm. is given an hour before the operation. This is often reinforced by giving from 0.30 to 0.36 c.c. of Magendie's solution by hypodermic injection. The best possible position for the administration of the anesthetic is that in which the patient sits on the side of the table, the body bent slightly forward, with the shoulders also rolled a little anteriorly and the head slightly bowed. The patient's feet should rest on chairs placed at such a height that they just allow the thighs to forms a right angle with the abdomen. An attendant should stand in front of the patient and provide the necessary support." To achieve success in this anesthesia we must block the eighth, ninth, tenth, eleventh and twelfth dorsal nerves, and the first lumbar and its two main branches, the iliohypogastric and ilio-inguinal nerves. On location of the landmarks, each one is painted with iodin or some other fairly indelible antiseptic substance. For intercostal injections, we locate a spot for needle puncture starting in its eighth space, usually opposite the angle of the scapula, and then

(3) Jour. Amer. Med .Ass'n., Mar. 29, 1924.

down in each successive space till we reach the twelfth nerve below the last costal border. These punctures are about 3.5 to 4 cm. from the midline of the back; roughly, a little more than two fingerbreadths from the spinous process. One must be sure that one has the right spinous process, as they sometimes are quite irregular. (Fig. 13.)

Fig. 13.—Injection of procain under 8th, 9th, 10th, 11th and 12th ribs and in the loin.

We now look for the landmarks of our lower abdominal block or, as some call it, the quadratus block. For this purpose, we take a point about 3 cm. from the spine of the first lumbar vertebra extending anteriorly, and then a point opposite the anterior end of the twelfth rib and above the anterior superior spine of the ilium. The lower landmarks are the anterior and posterior superior spines of the ilium. Over each one of these points we raise a wheal with a medium size Luer type syringe and needle, using 1 per cent. procain. For nerve blockings Labat needles of about 8 to 10 cm. length answer the purpose quite well.

The injections are started by inserting our needle first through the wheals in the intercostal spaces at right angles to the surface of the rib, down to its lower border, injecting as we go. When the lower edge of the rib is struck, we withdrew the needle a little and then incline it to an angle of from 40 to 45 degrees in the direction of the vertebral column. The needle is then forced over close along the lower anterior edge of the rib until we impinge on the body of the vertebra. This brings us close to the intervertebral foramen, and between the ribs and transverse process. The injection is continuous from the time the puncture is first made until we impinge on the vertebra, so that there is no concentration anywhere; nor is it necessary; 5 c.c. of the procain is used in each dorsal nerve block from the eighth to the eleventh. As the twelfth nerve is below the rib and its branches ramify a little more, it is wise to use 7 c.c. here.

The quadratus block is now started by injecting widely in all directions (but principally toward the center of this space), both superficially and into the deep planes, from the four points previously noted as the corners of this area. This effectually blocks all nerves that may in any way supply the superficial or deep portions of the abdominal well in the vicinity of any of our possible incisions.

Previous to making the incision, it is wise to test out all these areas for anesthesia; and, if necessary, reinjection may be made. When the renal pedicle is reached, traction often occurs; and when this causes pain, which may be of a nauseating type, it may be advisable to inject a little procain around it. In patients who are extremely nervous, the sight of an ether can and a mask with a few drops on it will often work wonders. The total amount of procain used should rarely be more than 80 c.c., or at the most 150 c.c. of a 1 per cent. solution.

The authors believe that in properly selected cases, paravertebral anesthesia is the method of choice for operations on the kidney, as it throws practically no burden on the unoperated kidney or any other vital organ.

SEDATIVES

Bromid

Bromid in Arterial Hypertonia. Having shown that essential hypertonia is often caused by vasoconstriction of nervous origin, K. Henius[4] has employed systematic bromid treatment with very good results. He administers the treatment for two to three weeks at intervals of three to four days. He observed frequently a diminution of blood pressure by 40 mm. Hg. and an improvement of all subjective disturbance. In view of the fact that this treatment not only relieves symptoms but also their cause, *i. e.*, vascular spasm, and prevents secondary injury to the blood vessels and the heart, such treatment is likely to be of great importance.

Acetanilid

Acetanilid—Some of Its Therapeutic Uses. Stephen Harnsberger[5] deplores that, beyond its value in reliev-

(4) Klin. Wochenschr., May 20, 1924.
(5) Amer. Med., May, 1924.

ing pain and its use as an antipyretic—which authors seem to think limits its scope of usefulness—it is rarely mentioned in medical literature. It is not generally known that *acetanilid is a reliable remedy in ulcerated and other inflamed conditions of the tonsils, throat and fauces.* The impalpable powder blown on the inflamed surfaces will ease, stop and cure these troubles quicker and with more comfort to the patient, than any other remedy. The author has used it for years; and people from many sections send for the "blow powder," as they call it, after it has been brought to their notice by those who have used it.

This is his method: make a tube of writing paper shaped over a long lead pencil, with the outer edge pasted down. Have the patient hold his breath and depress his tongue while the powder is blown quickly on the affected surfaces. At the same time caution the nurse not to draw the powder down her own throat. Patients should take no water or anything else into the mouth for at least half an hour. The action is local.

Acetanilid is almost a specific in preventing premature births. It has also done well internally in cerebral and cerobrospinal affections, allaying pain and restlessness and giving comfort and refreshing sleep. In selected cases, conjointly with acetanilid, codein sulphate is very valuable in nervous and irritable conditions. It is also very effective in the occasional irritable cough.

Phenobarbital

Phenobarbital Sodium in Hyperemesis Gravidarum. H. E. Miller[6] treated ten patients, five of whom were undoubtedly instances of pernicious vomiting, with 0.12 gm. of luminal sodium one hour before each meal, and the same dose at bedtime, given by mouth in all but three cases, in which the first doses were given hypodermically. In every case the relief was immediate.

(6) New Orleans Med. and Surg. Jour., May, 1924.

Neocinchophen and Cinchophen

Neocinchophen in Rheumatic Fever. Ralph H. Boots and C. Philip Miller[7] treated twenty patients suffering from rheumatic fever with neocinchophen administered by mouth at the rate of 1 gm. an hour until relief was secured, or until the occurrence of toxic symptoms due to the drug, such as tinnitus aurium, vertigo, abdominal distress, anorexia, nausea and vomiting, or excessive diaphoresis. At the appearance of toxicity, the drug was discontinued for that day. If sufficient therapeutic effect had not been obtained by the following day, the drug was again administered in the same manner. It was occasionally necessary to follow the same procedure for three or four days; but usually by the end of two days the optimum therapeutic and subtoxic dose could be ascertained.

As the initial dose was found to vary considerably, *e. g.*, from 0.1 to 0.3 gm. per kilogram of body weight of the patient, the authors feel that a procedure such as outlined above is the safest one to follow when it is desired to bring the patient as quickly as possible under the influence of the drug. When this object had been obtained, the dose was reduced to about two-thirds or one-half of that of the first day. In the early part of the work, the drug was continued in this smaller dose for from ten to fifteen days, and then abruptly discontinued. Later, the authors felt that it was better to diminish the dosage more gradually, and if the patient showed evidence of a relapse to increase it. In general, these patients received a much larger total quantity of this drug and were observed longer than those reported by other authors.

They conclude that neocinchophen acts as an antiarthritic and antipyretic agent in rheumatic fever in a manner similar to the salicylates. Among sixteen cases of polyarthritis, in three neocinchophen failed to relieve

(7) Jour. Amer. Med. Ass'n., Mar. 29, 1924.

the arthritis completely; two of these were relieved by salicylates. In five there was a relapse of arthritis when the drug was discontinued; and in eight, the relief was permanent. Among four cases of rheumatic carditis with fever, the antipyretic effect of large doses of neocinchophen was followed by distinct improvement of other symptoms. In order to obtain these beneficial results, a large dosage was required; and accompanying these large doses, toxic symptoms and signs of renal irritation similar to those seen with the salicylates, but milder in character, were encountered in three-fourths of the patients. Usually these signs of renal irritation disappeared with continued administration of the drug; but in six instances they persisted until the drug was stopped. One must therefore watch for the appearance of toxic symptoms in administering neocinchophen in the same manner as in giving the salicylates. Salicylates seemed slightly more effective in rheumatic fever; while, on the other hand, neocinchophen was the less toxic of the two drugs.

While the salicylates give satisfactory symptomatic results in most cases of rheumatic fever, neocinchophen is useful in some instances in which the salicylates fail to relieve the symptoms completely or the patient is so susceptible to their toxic exects that sufficient therapeutic doses cannot be given. Either drug may replace the other; and occasions not infrequently arise in which such substitutions may be of decided therapeutic value.

Lack of Antiphlogistic Effect of Salicylate, Cinchophen and Neocinchophen in Experimental Edema of the Head and Neck. P. J. Hanzlik and M. L. Tainter[8] produced edema of the head and neck by the hypodermic administration of freshly dissolved paraphenylenediamin hydrochlorid (called "para" in this article) to rabbits, using a dosage of 0.19 gm. per kg. With this dosage the majority of rabbits respond with a peculiar specific edema of the head involving the tongue, lips and orbital

(8) Jour. of Lab. and Clin. Med., Dec., 1923.

tissues, and a pouchy swelling in the submaxillary region and of the cervical skin. The tongue is large and thick and protrudes from the mouth, the nose is broad, the cheeks are full, and the eyes give the appearance of exophthalmos. There are usually a marked chemosis and considerable salivation. The effects appear anywhere from one hour to three hours after injection and last throughout the second day if the animal survives. The majority of animals die eventually, irrespective of dosage, and death is due presumably to intercurrent disease as a result of lowered resistance imposed by the action of the drug.

The results of their experiments do not indicate that salicylate, cinchophen and neocinchophen ameliorated the edema and blood concentration effects of "para" in any way whatsoever, and therefore, as antiphlogistics under these conditions they were negligible. This conclusion agrees completely with that of Lacquer and Magnus regarding the antiphlogistic actions of salicylate and cinchophen in the pulmonary edema produced by phosgene in cats, and with that of Heubner and Gildemeister for the antichemosis action of cinchophen.

The experimental evidence indicates that *these drugs do not exert a beneficial influence on inflammatory changes* including the swelling, edema, and exudate of joints in acute rheumatic fever through a direct, organotropic influence unless the inflammatory changes of joints in acute rheumatic fever are different from similar pathologic changes in other regions produced experimentally. But there is no reason to assume that this is the case. In the present state of our knowledge, the most satisfactory explanation of the mechanism of action of salicylate, cinchophen, and similar drugs in rheumatic fever, including the antiphlogistic action, is the symptomatic, that is, that the relief in this condition appears to be mediated through the antipyresis and analgesia produced by these agents.

Cinchophen Poisoning. Since cinchophen and its close derivative neocinchophen have been lauded as nontoxic drugs and are used extensively in gout and arthritis, it might be well to sound a note of warning against the indiscriminate use of both these substances. Cinchophen induces irritation of the digestive tract as well as generalized itching, eruption and edema of the skin, fever, headache, etc. Cinchophen and neocincophen in large doses, such as are necessary in the treatment of rheumatic fever, show injurious effects on the kidneys, and other undesirable by-effects similar to those obtained from the use of the salicylates, such as nausea, vomiting, dizziness and tinnitus. As a whole, however, the toxic symptoms are somewhat less severe than with the salicylates. Neocincophen is practically inert in the stomach, producing little if any gastric distress or intestinal disturbance. Its therapeutic efficiency is not less pronounced than that of cinchophen but it is liable to produce the same constitutional symptoms.

Moses Barron[9] reports the case of a man aged 44 who, after taking two 0.5 gm. tablets of cinchophen which had always previously relieved his pain, developed within ten minutes an itching and prickling sensation of the skin, soon followed by numbness and a feeling of complete paralysis, so that he fell to the floor and could not move. He did not lose consciousness and recovered in about half an hour. Three months after this he again took two tablets for the relief of the pain. Within five minutes he had the itching and prickling sensation of the skin followed by a general numbness of the body and a sinking spell and he dropped to the floor in an absolutely helpless condition. An hour after the onset of the attack he was lying in bed with deep, labored breathing; the face, arms and chest were a bright pink; the skin was moist, the extremities were cold, the finger nails and lips were deeply cyanotic. He appeared to be semiconscious, occasionally answering in a very weak

(9) Jour. Amer. Med. Ass'n., June 21, 1924.

voice. His pulse at the radials was just barely perceptible, at times entirely imperceptible, and no heart sounds could at first be heard. The blood pressure by the ansuculatory method gave very faint tones up to 75 mm. The diastolic pressure could not be made out. Within half an hour, the pulse became more perceptible and then gradually increased in intensity. The next day the patient was feeling as well as usual. [Neocinchophen is a remarkably harmless analgesic. It should always be preferred to cinchophen.—Ed.]

F. J. Scully[1] reports a somewhat similar reaction occurring after one 0.5 gm. cinchophen tablet, in which a chill occurred lasting from ten to fifteen minutes. This patient also had had a similar reaction sometime previously after taking a single tablet of cinchophen.

Opium

Opium in Cardiac Dyspnea. Claude Wilson[2] recognizes two types of dyspnea. The first is the ordinary dyspnea as an immediate consequence of exertion, in which opium is a somewhat dangerous drug. In the lesser phases it is seldom called for; while in extreme degrees, though it may produce restful sleep and consequent improvement, its administration may terminate in euthanasia. The second division of cardiac dyspnea comprises two subtypes, both of them paroxysmal in incidence—Cheyne-Stokes breathing and cardiac asthma. Oxygen administered in either case, and in sufficient quantity, will not only very generally give speedy relief but, if continued long enough, will often terminate the vicious circle which has somehow been established and the normal respiratory rhythm will reassert itself. But, apart from well-equipped institutions, it is only in exceptional conditions that oxygen is quickly available—at any rate, in sufficient quantity to allow of any thing like its adequate exhibition. The object of this com-

(1) Jour. Amer. Med. Ass'n., Feb. 23, 1924.
(2) Lancet, Dec. 22, 1923.

munication is to call attention to the fact, which does not appear to be widely known, that opium is not only in many cases an efficient substitute, but perhaps the treatment of choice. Almost invariably a very moderate dose, and often a very small one, given hypodermically, not only restored the normal respiratory rhythm—sometimes very quickly—but orthopnea was lessened or abolished, the fluid exuded into the bronchi in the asthma cases was absorbed, and these improvements endured for periods varying from days to months. Of course, general treatment including digitalis and restriction of effort has been resorted to in each case between the attacks. [In one case of advanced heart failure reported by the author in this article, and in a number of cardio-renal cases observed by the editor, both opium and oxygen failed to abolish the periodic rhythm, at least more than temporarily. The opiate was, however, necessary to give the patient a moderate degree of comfort.—Ed.]

Narcotics to Avoid Operative Interference in Diphtheritic Croup. Schlossmann[3] recommends in the treatment of diphtheritic croup giving, together with a sufficiently large dose of the anti-serum, enough narcotic such as Narkophin, possibly with a chloral enema, to induce complete rest and sleep during the critical first twelve to 24 hours until the antitoxin takes effect. This is accompanied by fresh air treatment, the bed being placed on the veranda or close to an open window summer or winter. During cold weather the child is well covered up and kept warm by means of hot water bottles. This treatment as a rule renders tracheotomy or intubation unnecessary. In a series of 92 children who in the past would have certainly been subjected to tracheotomy only 11 per cent. died; which is far less than would have occurred in spite of operative interference, in which mortality of almost 50 per cent. must be reckoned with. The rationality of this treatment depends on the fact that the

(3) Deutsche. Med. Wochenschr., No. 28, 1924.

resting organism can get along with very little oxygen and that children suffering from the sensation of want of breath and the fear of suffocation become excited and restless, thus greatly aggravating their condition, because of the greater requirement of oxygen when moving about than when at rest.

Heroin Prohibition. Just before last Congress came to a close, it passed a bill whereby the manufacture and importation of heroin is absolutely prohibited. This bill came before Congress as the result of a campaign carried on for the protection of addicts or those who, by virtue of an unstable nervous system, may become addicts. However worthy the object may be the result is, as the Therapeutic Gazette[4] points out, so far as addicts are concerned, practically *nil*, because nearly all the heroin that is used by addicts is smuggled and does not pass through the hands of pharmacists and physicians. On the other hand, from the standpoint of practitioners of medicine who have been deprived of a drug that has been found of great value by many and which meets indications no other drug affords, this legislation is to be regretted.

CARDIANTS

Digitalis

Maxims on Use of Digitalis. Sutherland[5] points out that digitalis is not called for in all cases of weak and rapid cardiac action, and that when not required it will do harm through possibly toxic action. Moreover, the patient may be needlessly alarmed when he discovers that digitalis has been given, for the public is now firmly convinced that the use of digitalis implies the presence of heart disease, and that heart disease means a liability to drop dead at any moment.

(4) Therap. Gaz., July 15, 1924.
(5) Lancet, Dec. 8, 1923.

The chief factor which interferes with the action of digitalis is a condition of active toxemia. Thus in Graves' disease we have a cardiac disturbance which would appear suitable for digitalis therapy, namely, a persistently rapid heart. If the disease is active, if the system is being poisoned by an excessive amount of thyroid secretion, the use of digitalis in full doses has no effect. When the active symptoms have subsided and the toxemic condition has gone, the heart may have been damaged, as shown by the presence of auricular fibrillation or a rapid rate. At this stage digitalis may be given; and, as a rule, with great benefit. In the case of other poisons, such as alcohol in excess, the same results will follow. *It is useless to give digitalis until all signs of active toxemia have subsided.* In acute pyrexial conditions, digitalis does not slow the heart and no benefit follows its use. Even in a disease of fairly fixed duration like lobar pneumonia, the author does not know of any series of cases showing definite evidence of benefit from digitalis. Repeated disappointment have led many to give up using digitalis in pneumonia.

If we contrast the two classes of cases, those in which digitalis may be expected to do good and those in which it may not, we shall find that digitalis is serviceable when the disturbance in the heart-rate arises in the cardiac tissues; and that it is not useful when the disturbance reaches the heart from without, *i. e.*, through the blood-stream or the nervous system. The therapeutic benefits of digitalis are obtained when the later manifestations of heart disease have appeared, and not in the acute inflammatory or actively toxemic stages. An examination of the heart can never, by itself, be made the basis of our treatment. A weak pulse will not decide the matter because no one ever felt a strong pulse when the heart was beating 140 times a minute. The sphygmomanometer is useless as a guide to be used for digitalis. In the typical case of auricular fibrillation there is no constant arterial pressure, for it becomes as

irregular as the action of the ventricles. Before treating the patient for cardiac failure we must have evidence that there is cardiac failure. Such evidence is to be obtained solely from the symptoms complained of by the patient and the signs in his tissues that the circulation is defective. In other words, a patient who requires digitalis has definite signs and symptoms such as edema in the lungs or extremities, engorgement of the liver, and congestion of the kidneys as manifested by a scanty amount of urine. The outstanding symptom is breathlessness, noticed at first on slight exertion, increasing by degrees to breathlessness even at rest, and orthopnea. When breathlessness is present, with or without some edematous effusion, and when the heart, on examination, is found to be the organ at fault, and when the ventricular rate is rapid, that is the time to give digitalis.

Digitalis has to be given in such amount as to produce the required effect, which is slowing of the ventricular rate. Speaking generally, for an ordinary effective course of digitalis, from 16 to 24 c.c., of the tincture spread over four to six days are required. The amount usually ordered per day is 4 to 6 c.c. according to the urgency of the patient's symptoms. When 12 c.c. in all have been taken, the amount is fixed at 4 c.c. per day until the heart-rate is slowed to 80, or until vomiting, headache, or diarrhea supervene. Very often the two occurrences are simultaneous, that is to say, nausea comes on and the heart-rate is found to be distinctly slowed.

While this treatment by massive doses may be useful in urgent cases, when the patient's distress is very great, it has the disadvantage that some patients are intolerant of digitalis and develop toxic symptoms on small amounts. If such a patient is treated with massive doses, the toxic phenomena ensuing may seriously interfere with the prospect of recovery. For ordinary cases which appear to be suitable for digitalis therapy, if 24 c.c. have been given without producing nausea or slowing of the heart-rate, it is advisable to stop the drug for 24

or 48 hours. If no change takes place during this time the drug may then be resumed for a few days in doses of 3 c.c. of the tincture daily. Children require much larger doses in proportion to their size. A child of ten or twelve years with a chronic rheumatic heart and rapid rate and failure of the circulation will take from 45 to 60 drops of tincture of digitalis daily, or its equivalent, with great benefit, if administered under the precautions given above for adults.

Dosage of Digitalis in the Form of Powdered Leaf. E. C. Andrus,[6] after several unsuccessful attempts to develop a standardized dosage on the basis of tinctures of digitalis, decided to use the dried leaf. The initial dose was 0.8 gram, and 0.2 gram was administered every four hours thereafter. This dosage was maintained until there was evidence of pronounced clinical improvement or until some of the minor toxic symptoms of digitalis developed. The first subjective symptom noticed was usually loss of appetite. This was taken as an indication for stopping the drug, at least temporarily. The amount required to produce definite evidence of physiological action was surprisingly uniform with dried leaves. Definite evidence of therapeutic effect was found in 95 per cent. of the cases after a dose amounting to 1.5 grams per 100 pounds of body weight.

Massive Doses of Digitalis in Auricular Fibrillation Without Heart Failure. Julius Jensen[7] shows on the accompanying chart the average results obtained in seven cases of auricular fibrillation without heart failure from three large doses of digitalis given as follows. (Fig. 14.)

If the patient was under the influence of digitalis on admission, he remained without medicine for at least fourteen days. He was then confined to bed, and the apex beat was repeatedly counted with stethoscope and charted. The urine was measured six-hourly, and the

(6) British Med. Jour., Apr. 19, 1924.
(7) Lancet, Apr. 12, 1924.

patient was observed in this way for three to four days before any drug was administered. On the morning of the day of administration he was again examined, and absence of signs of failure confirmed. One or one and a half drachms of a standardized tincture of digitalis was then administered. Six hours later the second dose —1 drachm—was given, and six hours later still the third and last dose, another drachm.

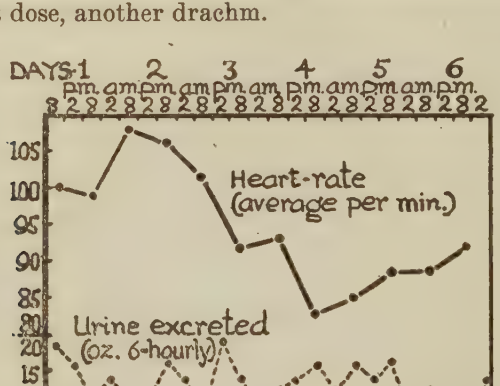


Fig. 14.—Chart showing the average heart-rate (continuous line) and amount of urine excreted (interrupted line) before and after digitalis.

The heart-rate was in most cases affected to some extent on the evening of the day of administration, about twelve hours after the first dose had been given, and the average fall in rate by this time was ten beats per minute. This fall was maintained the next morning, and later on in that day a further fall of ten beats per minute occurred, though no more digitalis had been given. The quality of the pulse was much improved, the volume being larger. In a few cases coupled beats appeared temporarily. This control of rate, however, was not very stable, as counts taken after meals or after slight exertion or excitement nearly always showed that the pulse

had risen towards its original rate. Very often, also, there was a relapse lasting for a few hours without any apparent cause. The total duration of the effect was from four to fourteen days.

Digitalis had no definite diuretic effect on any case. This observation confirms the general view that digitalis exerts little or no diuretic effect (even in large doses) unless edema, obvious or masked, is present.

The patients all felt better and said that they had less palpitation. Apart from occasional couplings of the pulse in two cases there were never any indications of overdosage. Nausea and vomiting were never seen, a fact of special interest, tending to show that the vomiting which sometimes occurs early in the administration of digitalis in heart failure depends far more upon the failure of the heart than upon any irritant effect of this drug on the stomach.

Digitalis in Pneumonia. An editorial* in the Therapeutic Gazette calls attention to a communication to the Archives of Internal Medicine by Levy, who using the *x*-ray in a study of 21 cases, found enlargement of the heart in 61.9 per cent., whereas in those patients who received digitalis, dilatation occurred less frequently. In bronchopneumonia, cardiac dilitation was less frequent than in lobar pneumonia, being observed in only 25 per cent. of the cases, but the two patients in this group who received digitalis showed no dilatation.

The writer of the editorial has long practiced the administration of moderate doses of digitalis from the beginning to the end of the attack in association with belladonna, commonly employing 10 minims of the tincture every eight hours and 10 minims of the tincture of belladonna every four hours, unless some contraindication to either drug seemed to exist, and the results which he has obtained have led him to believe that in the absence of specific treatment this method has pro-

(*) Therap. Gaz., Mar. 15, 1924.

duced advantageous results. This dose is large enough to have definite action upon the heart without cumulative effect, and even if continued over the full week or ten days of the illness, is not capable of acting as a toxic agent.

Digitalis Elimination. Standardization in digitalis therapy has made a long stride by the advent of the cat unit determination of activity and the application of this unit to digitalis dosage in man. While it is commonly recognized that activity and not quantity is the rational basis for administration, it seems less commonly appreciated that in point of standardization the drug activity is only one-third of the problem. Absorption and elimination need also to be considered.

Pardee (1919) arrived at the conclusion that the average daily elimination of digitalis in man is 22 minims of a tincture, the activity of which was 1.25 c.c. to the cat unit. H. Gold[8] has observed about 75 patients suffering with chronic cardiac disease and heart failure requiring, on the average, about 30 minims a day of a preparation with the activity of a cat unit in 0.75 c.c., to maintain optimum improvement over weeks and months. It is obvious that one cannot say whether absorption or elimination accounts for the fact that one preparation required two and a half times the dose of the other in point of activity to maintain digitalization. We must conclude, however, that, though the activity be the same, different lots of the tincture prepared from different lots of the crude drug will in all probability vary in their rates of elimination.

Rectal Digitalis Administration. Robert L. Levy[9] administered digitalis by rectum 26 times to nineteen patients with auricular fibrillation and to one patient with ectopic auricular tachycardia; also in twelve surgical cases following operation. The preparation employed was an aqueous solution of a purified extract of digitalis

(8) Arch. Inter. Med., November, 1923.
(9) Arch. Int. Med., June 15, 1924.

leaves. One c.c. contained the equivalent of 0.1 gm. of powdered leaf. The amounts given ranged from 8 to 20 c.c. administered at one time. The average time necessary for an unmistakable initial effect on rate was two hours and thirty-five minutes. The average time which elapsed before a maximal effect on rate was apparent was nine hours and thirty minutes. A desirable therapeutic effect was apparent in every instance. In many of the patients, the results were dramatically rapid and beneficial. Rectal digitalis therapy is intended to supplement, not supplant, the oral method of administration. It is useful in the presence of nausea and vomiting, or after surgical operation, when oral medication is not feasible. The dose is comparable to that employed when a large single dose is given by mouth.

F. A. Willus[1] reports that, when he slowly instilled into the rectum, after a cleansing enema, 6 c.c. of the tincture of digitalis in 100 c.c. of salt solution and repeated this daily, a distinct effect of digitalis was evident within one or two days. With three daily rectal instillations of 2 to 2.5 c.c. of tincture in 60 c.c. of salt solution, from three to five days were required to obtain the same results.

Intravenous Injection. G. Canby Robinson, Paul D. White, Cary Eggleston and Robert A. Hatcher[2] protest against the intravenous use of digitalis bodies as an emergency measure in cases of sudden heart failure when a careful study of the heart has not been possible. Auricular fibrillation is the one condition in which there is general agreement that the digitalis bodies are indicated. This condition is characteristic clinically by a totally irregular action of the heart, with a marked acceleration of the ventricular rate, and with numerous contractions that fail to produce a palpable pulsation in the radial artery. The digitalis bodies are also indicated in auricular flutter when the ventricular rate is excessive, both

(1) Northwest Med., March, 1924.
(2) Jour. Amer. Med. Ass'n., Aug. 16, 1924.

from the fact that these drugs tend to cause a disappearance of the abnormal auricular activity and because they bring about an improvement in cardiac efficiency by ventricular slowing.

Premature contractions, or extrasystoles, have long been known as one of the early signs of excessive digitalis medication. In spite of this fact, their existence in a patient who has not recently received digitalis should not be taken as a contraindication for the use of this drug. In most cases, extrasystoles are an incident in, rather than a cause of, cardic decompensation, and their presence may be neglected in considering the probable efficiency of digitalis therapy.

The digitalis bodies have proved of no constant value in paroxysmal tachycardia, although in prolonged attacks in which evidence of myocardial failure may supervene, digitalis should be used with the hope of improving the cardiac efficiency even without influencing the excessive cardiac rate.

The use of the digitalis bodies is justified when any symptom or group of symptoms is present which can be accounted for by no other cause than myocardial insufficiency. Dyspnea, chest pain on exertion, orthopnea, edema, cyanosis, congestion of the lung bases, liver or kidneys, with hydrothorax especially of the right pleural cavity alone may be taken as indications for the use of the digitalis bodies, especially when there is evidence of cardiac dilatation, a departure from the usual level of blood pressure and alteration in the character of the heart sounds. In cases with normal rhythm, however, the digitalis bodies are to be used with hope rather than assurance. Each case should be studied with care, as some of these patients are unusually susceptible to the toxic effects of these drugs. It is for this reason that these patients especially should receive digitalis by oral administration rather than by intravenous injection.

A digitalis preparation should be used intravenously or intramuscularly only in those cases in which it is

imperative that the therapeutic effects shall be induced within two hours or less; that is, within less time than they can be induced with a fair degree of certainty by oral or rectal administration.

The only contraindication for oral administration other than the necessity for haste in inducing the therapeutic effects is the presence of nausea or vomiting. In such cases, digitalis may be administered by the rectum, as it has been found that it is absorbed from the rectum about as rapidly as after oral administration. Rectal dosage may be calculated in the same way as oral, because the rate of aborption has been found to be so nearly the same.

Intravenous (or intramuscular) dosage of crystalline ouabain or amorphous strophanthin need rarely, if ever, be calculated for saturation. One dose of 0.5 mgm. as a maximum may be given in the case of an adult; rarely, two or three such doses at intervals of six hours. In an emergency, one dose of 0.5 mgm. suffices, digitalis being given by mouth in doses of 0.3 gm. of the powdered leaf or 3 c.c. of the tincture every four hours until the therapeutic effects or signs of toxic action are induced. In cases of nausea and vomiting not the result of digitalization, ouabain or strophanthin may be given intravenously or digitalis by the rectum.

The oral administration of digitalis in the form of the standardized powdered leaf, infusion, or tincture, meets every requirement of digitalis therapy, with the exception of those relatively infrequent cases in which immediate r e l i e f (within two hours) is imperatively demanded, or when nausea or vomiting precludes the oral method. Great care must be exercised in this method of using any digitalis body in patients who have recently received digitalis or any of its substitutes.

Ouabain may be kept in hard glass ampules or in buffered solution for several months without appreciable change. Or it may be obtained in hypodermic tablets containing 0.1 mgm., 0.25 mgm., and 0.5 mgm. These

may be dissolved in 1 c.c., 2.5 c.c., or 5 c.c. of sterile physiologic sodium chlorid solution and injected intravenously or intramuscularly.

The proprietary preparations of digitalis and its principles have no advantage over digitalis, crystalline ouabain, and amorphous strophanthin.

Strophanthus

Strophanthus Inhalation. In view of the difficulty of introducing digitalis into the circulation by oral administration when there is passive congestion of the alimentary tract by reason of cardiac decompensation, the injection of digitalis bodies is resorted to under these circumstances. H. Januschke[3] reports that, when in a military hospital under his direction during the late war, digipuratum solution which they used for injection purposes was unobtainable, he resorted with great success to the inhalation of tincture of strophantus in doses of 12 to 20 drops mixed with 30 c.c. of hot water and sprayed by means of a Siegle apparatus. In calculating the dosage the author considers 12 drops as corresponding to about 0.5 c.c., the maximum single dose of tincture of strophantus, of which he believes half is probably lost during the inhalation. The treatment was repeated twice daily, and by means of it cardiac compensation was established within a few days. He also reports a case of an elderly woman with cardiac edema and dyspnea with whom digitalis by mouth was useless and who had refused injection in whom this inhalation treatment was successful. The advantage of this mode of administration consists in the fact that the circuitous route through portal vein and hepatic capillary system is avoided.

Glucosides of Squill

Favorable results are reported from the use of isolated glucosides of squill recently introduced into the market.

(3) Ars Medici, December, 1924.

This might reestablish the use of squill, as its disuse might have been due to unreliable preparations. *Scillaren* is a pure crystallised glucoside, soluble in water, producing a stable solution. It is marketed in ampules representing 200 and 800 frog units for subcutaneous and intramuscular injection, and in tablets representing 600 frog units.

E. Jenny[4] found that 1 kg. of dry substance of freshly prepared squill contains 8,000,000 frog units, while the same quantity of digitalis contains only 2,000,000 frog units. Hence, according to frog units, squill is a highly efficient drug.

E. Körner[5] reports that the action of scillaren is similar to that of strophanthin. It strengthens the general action of the heart muscle, diminishes the pulse rate, increases its size, lowers the blood pressure, and corrects irregularities of the rhythm. It seems to have a specific action on the diastole, being superior to other cardiants in this respect. It is eliminated more quickly than digitalis; hence there is no danger of cumulative effects, even on prolonged use. It is well tolerated regardless of previous medication. The author believes that tablets give as good results as intravenous injections and advises to give four tablets daily, each of 600 frog units. The maximal effect is noted by the second day. On intravenous administration the effect on the pulse rate is noted shortly after administration, the diuretic effect somewhat later. Where no diuretic action is obtained by scillaren alone, the author recommends a combination of scillaren 1.1 c.c. and novasurol 2.2 c.c. intravenously. Scillaren does not act upon the normal heart nor upon hearts that are not decompensated. Its main indication is cardiac insufficiency, especially where digitalis was not, or is no longer effective. It is contraindicated for patients with a tendency to angina pectoris and in acute nephritis.

(4) Schweizer. Med. Wochenschr., June 1, 1922.
(5) Klin. Wochenschr., June 10, 1924.

E. Boden and P. Neukirch[6] found scillaren most effective in myocarditis. They obtained a general improvement and loss of weight in three cases where digitalis and strophanthin were ineffective. In one case auricular fibrillation disappeared after two days' use of scillaren and reappeared the third day after scillaren was abandoned. The action on the rhythm was very striking. No favorable results were obtained in mitral lesions and cardiac insufficiency following renal disease.

G. Perrin[7] also reports that scillaren stimulates the tone of the heart, strengthens the systole, prolongs the diastole, increases the amplitude of the pulse, increases the blood pressure slightly, and causes an abundant diuresis. No ill effects were noted. He advises 1 to 3 tablets of ½ mgm. each be given twice or three times daily according to circumstances. Gastric disturbances are very rarely noted; but if so, he recommends subcutaneous or intramuscular injections of 1 to 3 ampules daily, each containing the same dose. He believes that scillaren has its place where danger of digitalis cumulation is feared, and where prolonged diuresis is desirable.

E. Ahlswede and W. Busch[8] consider scillaren a good remedy in cases in which there is more or less considerable weakening of the heart muscle associated with edema, and disturbance of renal secretion. It should be avoided in coronary sclerosis.

E. Boden[9] reports good results with *Scillicardin*, another new preparation of squill. He emphasises the strong effect upon the tone, especially upon organic decompensated heart disease and edema and absolute arthythmia. The effect upon the heart rate of arteriorsclerotic myocarditis is, even with small doses (three times 5 to 10 gm.), so great that this remedy can be used for functional tests, as in myocarditis there is a particular tendency to bradycardia on vagus stimula-

(6) Deutsches. Arch. f. klin. Med., Apr. 30, 1923.
(7) Gazette des Hopitaux, July 10-12, 1923.
(8) Clinical Med., April, 1924.
(9) Klin. Wochenschr., May 13, 1924.

tion. The tachycardia of fever and of tuberculosis can be almost regularly reduced to normal.

Quinidin

Clinical Value of Quinidin. C. Sidney Burwell and Francis R. Dieuaide[1] report that of sixteen cases of auricular fibrillation treated with quinidin sulphate, fourteen (88 per cent.) reverted to normal mechanism, and that regular rhythm has persisted in eight of these patients; in six for more than six months. In the cases remaining persistently regular there has been marked improvement in the patient's health. Death occurred in three patients in one shown to be due to embolism from an intra-auricular thrombus.

Therefore, in patients with auricular fibrillation who cannot be brought to a satisfactory degree of circulatory efficiency by the usual therapeutic measures, an attempt to cause reversion to normal mechanism by quinidin is justified by the hope that the patient's health will be improved thereby. It is well established that the change in rhythm can be effected in at least 50 per cent. of the cases. Two grams of quinidin sulphate may be administered daily without the production of severe toxic symptoms, and such a dosage results in a higher percentage of successes than does a smaller dosage. So far as is known at present, the danger associated with the use of this drug lies not in its direct effects but in embolism from an intra-auricular thrombus following the onset of normal auricular activity.

John Wyckoff and Meyer Ginsberg[2] report one case of sudden collapse and two cases of sudden death in a series of 26 unselected cases of auricular fibrillation, of which 68 per cent. developed sinus rhythm after receiving quinidin sulphate. Certain of these cases were kept free from attacks for long periods of time by a daily ration of quinidin. They employ the following

(1) Arch. of Int. Med., April, 1923.
(2) Boston Med. and Surg. Jour., May 8, 1924.

method: test doses of 0.2 gm. were given the day before full dosage was instituted. The next day 0.4 gm. was given every two hours until five doses had been given, unless the patient returned to normal rhythm or developed toxic symptoms before five doses had been given. If the patient did not develop sinus rhythm or toxic symptoms, this dosage (0.4 gm. every two hours for five doses each day) was continued for a week, and in one case, nine days. Inasmuch as, in spite of these precautions, one case of sudden collapse and two cases of sudden death occurred in their series they conclude that a test dose of 0.2 gm. of quinidin sulphate repeated in two hours followed by no symptoms of toxicity is no indication that the patient may not become toxic with larger doses of the drug.

Action of Quinidin on Amphibian Heart. J. A. Waddell and Morris Cohen* have demonstrated by experiments on the hearts of turtles and frogs that, as is generally held, quinidin is a depressant to the heart, producing effects through action on the musculature of the heart, including that of the conducting system. With moderate dosage, there is no evidence of permanent tissue damage, all effects being abolished by withdrawal.

Quinidin Action on Striped Muscle. J. G. Brody and Torald Sollmann[3] find by experiments on isolated frogs' muscles that an independent rhythm is produced in the tetanized quinidin muscle due to a lengthening of the refractory period. It is obvious that the results obtained in the experiments with quinidin on striped muscles are quite parallel to the clinical results with quinidin in auricular fibrillation. In both cases *the prolongation of the refractory period makes the muscle independent of a rapid rate of stimulation* that ordinarily produces more or less complete tetanus and enables it to adopt the slower rhythm and more extensive

(*) Jour. Labor. and Clin. Med., September, 1924.
(3) Arch. Internat. de Pharmacodynamie et de Thérapie, p. 481, 1923.

excursions that are so much more efficient for working a pumping mechanism.

The investigation by means of the skeletal muscle, however, shows a further very important fact, which is not so easily analyzed in the patient, that is, the refractory period is necessarily accompanied by, in fact is due to, depression of the muscle itself. In the heart, this may be obscured by the fact that the slowing permits more rest as well as greater mechanical efficiency for a given expenditure of energy by the muscle. The balance between the benefits of slowing and the detriments of diminished contractility varies with conditions, and this balance determines whether the efficiency will be increased or diminished. In this respect again, the muscle experiments show the cause of a clinical experience, *viz.* the superiority of quinidin over quinin. Both act alike in principle but with quinin the depressed contractility is more marked than the prolongation of the refractory period.

It must not be overlooked, however, that *the mechanism of the action of quinidin depends on depression* which may easily become detrimental instead of beneficial to the efficiency of the heart. This probably depends largely upon the state of the tissue. Most hearts have sufficient reserve to compensate the depression, and may therefore be benefited by regularization of the contraction; but hearts that are fatigued, overloaded by distention, or otherwise weakened, may succumb to the depression; for these states greatly exaggerate the quinidin depression as shown by the muscle experiments. This is probably one cause, at least, of the clinical fatalities. It indicates extra caution in the administration of quinidin in such cases; and it is also very probable that smaller doses would suffice to produce the therapeutic effect than are required for more vigorous hearts.

It appears also not improbable that the *combination of quinidin with digitalis treatment may add to the safety;*

for digitalis would tend to counteract the diminished force of the heart, probably without hindering the effect of the quinidin on the refractory phase. This is realized in the usual clinical practice, where quinidin is preceded by a course of digitalis. However, the suggestion deserves more direct investigation.

In any case, these considerations emphasize that *the heart should be rested and spared as much as possible in preparation for and during the administration of the quinidin.*

Effect of Light on the Action of Quinin and Quinidin. David I. Macht and Elmer J. Teagarden[4] studied the effect of light on the behavior of normal rats and of rats injected with solutions of quinin and quinidin sulphates in respect to their behavior in the circular maze. It was found that the pharmacologic activity of quinin and quinidin sulphates was greater in animals exposed to light than those kept in darkness; also that the absolute lethal doses of quinin and quinidin were smaller for animals kept in light than those kept in darkness. Exposures merely to sunlight or ultraviolet radiations from a quartz lamp produce either no effect or a stimulating effect on normal rats.

RESPIRATORY STIMULANTS

Lobelin

Lobelin as Respiratory Stimulant. This alkaloid of lobelia, which has been shown to possess the specific action of increasing the sensitiveness of the respiratory center to carbon dioxid, has been used as a respiratory stimulant in asphyxia of the newborn as well as in that occurring in pneumonia and various intoxications, and also in the respiratory collapse of anesthesia. W. Grill[5] reports two cases from surgical practice with marked

(4) Jour. Amer. Med. Ass'n., Nov. 3, 1923.
(5) Klin. Wochenschr., Jan. 1, 1924.

depression of respiration that occurred either from hemorrhage or from hemothorax in which intravenous (1 case) and intramuscular (1 case) injection produced remarkably favorable, apparently life saving results.

TOXICOLOGY

ENDOGENOUS POISONS

Anaphylaxis

Allergy. P. J. Hanzlik[6] believes that the anaphylactic and anaphylactoid phenomena, collectively the allergic phenomena, appear to rest on a common basis, namely, on disturbances in the physical and chemical (colloidal) mechanism of the blood and tissues. Exceptions to this are the period of incubation and the hyperexcitability of isolated smooth muscle that appear to be peculiar to protein anaphylaxis, and some discrepancies in the histologic changes; but these differences may be explained and reconciled on a physical basis. In view of sundry difficulties, the exact explanation of the physical-chemical disturbances is not yet at hand, though it is believed that such disturbances mediate cellular stimulation and depression and hence alteration in normal functions commonly recognized as symptoms or "reactions."

Corpuscles, plasma and endothelium of the vessels will be affected immediately, and then the tissues and organs, among which the heart and lungs come first. The final result will depend on the influences of several factors, such as the nature of the agent, its dosage or concentration, the state of physiologic functions, the operation of defensive mechanisms (absorption, excretion, destruction, etc.), and perhaps other factors. The outcome may be no demonstrable change, stimulation or depression, and the therapeutic result no change beneficial or detrimental.

(6) Jour. Amer. Med., Ass'n., June 21, 1924.

Several of the agents inducing "anaphylactoid phenomena" are employed empirically for the alleviation, if not cure, of disease conditions whose symptoms they reproduce wholly or partly (synergistic action). This is followed by the alleviation or suppression of the symptoms subjectively and objectively (antagonism). Curiously, diseases with unknown etiology (rheumatic fever, arthritides of various kinds, etc.), and symptoms of unknown origin, especially pain, fever, and chronic inflammatory processes, appear to respond most favorably. Apparently the physical and chemical changes resulting in the blood and tissues from the administration of these agents are responsible for the benefits derived from widespread alterations in cellular function, including increase in capillary permeability, which would aid in removing edemas and chronic inflammations, facilitate exchange of metabolites, increase the metabolism, etc. On the other hand, the results may be alarming and even fatal. This might be expected from the flocculations, agglutinations, embolism, and thrombosis, provided these are sufficiently marked, extensive, and present in important organs (lungs, brain, heart), resulting in sudden death, or asphyxiation and death from the capillary stasis and blockage.

The study of allergic phenomena teaches that almost any agent may be the cause of a reaction. Even isotonic sodium chlorid solution is not physiologic, but it is not as injurious as some other agents and solutions.

An agent injected intravenously may be temporarily beneficial to one function, but detrimental to others and to the organism as a whole. This is illustrated by the intravenous use of acacia in shock and similar conditions. By the use of acacia, a single function may be improved; that is, the level of blood pressure may be raised and maintained at a high level for a time. However, the net result for the organism is no better, and is usually worse, than by other methods of treatment, injurious effects in and greater mortality of animals

than from other solutions having been demonstrated, and also severe reactions and death in patients.

The intravenous effects of agents cannot be predicted from their physical and chemical properties and from their physiologic effects when given by mouth. For instance, agar, which is chemically inert and harmless when given by mouth, produces violent reactions and even death when injected intravenously in minute doses. Such common agents as hexamethylenamin, iodid, and salicylate cause definite chemical and physical changes in the blood of animals. These changes, taken together with the symptomatic and histologic changes from the same agents, indicate that they are disturbing and injurious to important functions and tissues when administered intravenously. There is *no justification for the intravenous administration of such agents as hexamethylenamin, sodium iodid, and sodium salicylate*, because their ordinary systemic effects are readily and promptly obtained from oral administration. On the contrary, other and more detrimental effects may be obtained from intravenous administration.

Sudden Death Associated with the Injection of Foreign Substances. R. W. Lamson[7] quotes statistics of W. H. Park (1921) that one death occurred for every 70,000 persons injected; and these deaths, with possibly two exceptions, followed the first injection. Such statistics, covering as they did about 350,000 persons treated with serum, indicate most clearly the almost insignificant numerical possibility of the occurrence of a fatal case. If operative surgery is indicated in the treatment of a patient and there is not definite contraindication for the use of ether there is no hesitancy about giving this anesthetic. Yet statistics would indicate that fatalities from ether *per se* are from seven to ten times more frequent than those due to the use of diphtheria antitoxin. Such facts, however, should not make one any less careful in the admin-

(7) Jour. Amer. Med. Ass'n., Apr. 5, 1924.

istration of foreign serums, and every known precaution should be taken for the protection of the patient. On the other hand, exaggeration of the danger of serum treatment has often caused delay in giving the serum, which is also an injustice to the patient.

As a result of his own studies, Lamson arrives at the conclusion that the total number of reported cases of so-called "fatal anaphylaxis" is much smaller than generally believed. Coincidentally with an enormous increase in the use of foreign serums and other proteins in the treatment of patients, there has been a very marked reduction in the number of fatal cases per unit of population treated.

Although the probability of a fatal reaction occurring is slight, it must be considered. A negative skin test may not be an absolute index of the reaction capacity of the patient. About 34 per cent. of the cases give a definite history of asthma or hay-fever. In several instances this condition was exaggerated by proximity to horses. In eight cases there was a history of a previous injection of foreign protein.

Diphtheria intoxication may not preclude the possibility of a fatal result after serum injection.

The exact mechanism involved in these cases is not easy to define. There is some evidence to indicate that the serum injected played no specific part in the death of the patient. On the other hand, status lymphaticus may be an incidental finding in a case of true anaphylaxis.

In a few of the observed cases, the amounts injected were so minute that it is difficult to believe that the nature of the injected substance could have had very much to do with the fatal result. One is inclined to assume individual physiologic peculiarities on the part of the patient as the predetermining factor.

[The careless routistic injection of antiserum in cases in which there is only a remote possibility that it may do good cannot be too severely condemned, as it may

sensitize the patient to horse serum in such a way that, when at some time in the future its use is imperatively demanded, the patient suffers from symptoms of induced intolerance.—Ed.]

Anaphylactic Internal Secretion of Liver. W. H. Manwaring, James R. Enright, Dorothy F. Porter and H. Bing Moy[8] find that a sharp contraction of the urinary bladder takes place during the first two minutes of typical canine anaphylactic shock, which does not occur in dehepatized anaphylactic dogs. They conclude that the typical anaphylactic bladder contraction is due to chemical products (hepatic anaphylatoxins) explosively formed or liberated by the anaphylactic liver, products having a histamin-like effect on the urinary bladder.

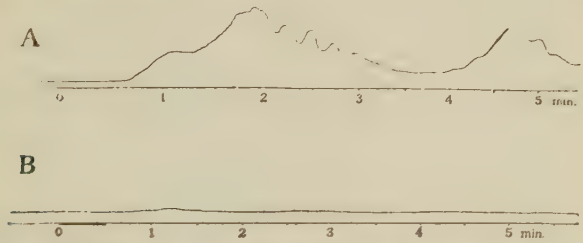


Fig. 15.—Effects of dehepatization on anaphylactic rectal reactions: A, intact dog; B, dehepatized dog; heavy base line, intravenous injection 1 c.c. horse serum per kg. weight.

They also find[9] that marked increases in gastro-intestinal tone takes place during the first two minutes of typical canine anaphylactic shock. These tonal reactions likewise do not take place in dehepatized anaphylactic dogs. (Fig. 15.) They are evidently also due to hepatic anaphylatoxins. It is possible that the hepatic anaphylatoxin is but an exaggerated amount of a normal hepatic internal secretion, an hepatic hormone, whose main function it is to cause rapid evacuation of the gastro-intestinal tract on the absorption of toxic products from the intestine.

(8) Jour. Amer. Med. Ass'n., May 10, 1924.
(9) Ibid., Nov. 8, 1924.

Allergic Manifestations in Pharmacists. M. M. Peshkin[1], as a result of his own experience, a study of the literature, and of a questionnaire sent to fourteen manufacturing pharmaceutic houses, arrives at the conclusion that sensitization to drugs is more common than one is led to believe from the few reports in the literature. Ipecac is the most common cause of bronchial asthma in pharmacists and pharmaceutical workers. Next to ipecac, the commonest causes of bronchial asthma in pharmacists are podophyllin and pokeroot. The handling of emetin solution and vanilla beans causes skin manifestations characterized by urticaria of the forearms and hands, with intense itching. Synthetic drugs and desiccated animal gland extracts apparently play no role in the causation of bronchial asthma, except that by inhalation they may induce an asthmatic attack by mechanical irritation. Rhubarb and lycopodium hypersensitiveness are unusual causes of allergic manifestations in pharmacists.

Guanidin

Guanidin and Arterial Hypertension. Ralph H. Major[2] believes that, in collaboration with Walter Stephenson, he has succeeded in demonstrating the existence of a metabolite, pressor in type and producing a sustained rise in blood pressure unequaled by any hitherto described substance. While urea, uric acid, creatin and creatinin had no constant effect on the blood pressure, the guanidin bases have a very powerful pressor effect.

The blood pressure in dogs is often doubled or even tripled within a few minutes after the intravenous or intramuscular injection of from 0.1 to 0.2 gm. of methyl-guanidin sulphate per kilogram of body weight; this high pressure persisting often from four to five hours. The rise is due, in part at least, to peripheral

(1) Jour. Amer. Med. Ass'n., June 7, 1924.
(2) Ibid., July 12, 1924.

vasomotor action. In addition to these effects on the blood pressure, the guanidin compounds also produce a marked decrease in the respiratory rate and a slowing of the pulse with an increase in the amplitude of the heart beat. When toxic doses are given, the blood pressure, after a preliminary sharp rise, often falls, the respiration may be paralyzed, and the heart beat usually becomes extremely irregular. Also, as is well known, toxic doses of these compounds will produce twitchings very similar to those seen in tetany; and larger doses may cause severe convulsions.

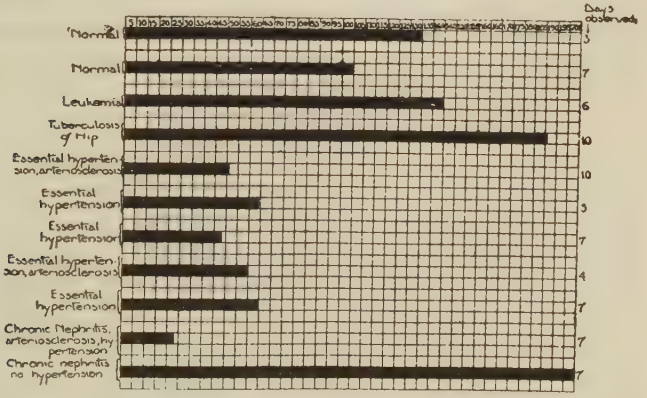


Fig. 16.—Daily excretion of guanidin bases, in milligrams, calculated as dimethylguanidin, in a series of patients and normal controls; there is diminished excretion in patients with arterial hypertension.

The excretion of guanidin bases in the urine of dogs poisoned with uranium nitrate was next studied. After the development of a severe nephritis with high values for blood urea and blood creatinin, a marked and gradual diminution in the output of the guanidin bases occurs, which persists until the death of the animal.

The excretion of guanidin bases was then studied in the urine of normal persons and of patients suffering from diabetes mellitus, chronic nephritis, essential hypertension and other diseases. All, while under

observation, were placed on a meat free diet. A summary of the results (Fig. 16) shows that, while normal persons and patients with a normal temperature and normal blood pressure have shown an average daily excretion of 100 mgm., the patients with a high blood pressure show a marked diminution in the excretion of guanidin bases. Further observations must show whether this is a constant finding. It seems quite possible that kidneys badly damaged by chronic nephritis or only slightly damaged by arteriosclerosis or by a small vessel sclerosis might be unable to excrete properly these substances having such a marked pressor effect. Such a retention of guanidin bases, unless they were utilized or destroyed, might result in an elevation of blood pressure.

Histamin

Histamin, Cause of Intestinal Intoxications. It is often stated, even in recent articles on the subject, that intestinal autointoxication is largely a matter of speculation as no poison has thus far been identified as being capable of producing the results ascribed. Hence it is of importance to point out that the toxicity of histamin has been definitely established, that its elaboration in the colon is of frequent occurrence and is often associated with organic and functional pathologic states, and that the eradication of histamin by dietetic, chemical, and *B. coli* implantations frequently results in clinical cures. This is the claim of Clarence W. Lieb[3], who reports that out of 320 stools examined during the past two years 278 showed high histamin reactions. Most of the stools examined were from patients showing some form of chronic physical disability. Thirty per cent. of the stools in which histamin was found showed red blood coloring matter in conspicuous amounts, and 92 per cent. of these stools

(3) New York State Med. Jour., Feb. 1, 1924.

showed large amounts of mucus (after straining the stools through gauze). Colon bacilli were present in minimal numbers in these histamin stools.

The newer bacteriologic investigations as to the elaboration of toxic split products in the intestine leads to the conclusion that intestinal autointoxication is not a new bacteriological infection but a matter of bacterial activation with toxin formation. This changes our entire conception of intestinal toxemia. The problem resolves itself into a matter of keeping the contraindicated sugars out of the diet, or at least from reaching the lower bowel. A high residue diet, by mechanically carrying sugars to the colon; hyperperistalsis, by hastening the intestinal contents from stomach to colon; and hyperacidity, which inhibits starch digestion are factors which must be dealt with in the correction of intestinal toxemia.

For dehistaminizing patients the author recommends:

1. Gastro-intestinal rest. This is accomplished with a low residue diet, peristaltic inhibition by means of atropin or benzol benzoate, and, as histamin is only formed in the presence of acid, gastro-intestinal alkalinization with the following powder:

Calcium Carbonate } of each	2.0
Calcium Lactate }	
Heavy Magnesium oxid	0.6
Kaolin (highly absorbent)	15.0

Label: one powder in one glass of water three times a day before meals.

2. Colonic lavage, with ½ per cent. monohydrated sodium carbonate to kill Gram negative organisms—these being the chief bacterial offenders in the colon—and a 2 per cent. kaolin suspension which has the property of making histamin inert rendering bacterial toxins harmless and changing the bacterial from a proteolytic to an aciduric type.

3. *Bacillus coli* implantation with suspensions of known strains of high indol-producing *B. coli* in a dextrin solution implanted in the colon until thorough

colonization is established, as it has been shown that when *B. coli* are allowed to metabolize the aminoacid histidin, the toxic amin histamin is not formed.

Of 318 patients treated by these methods 242 showed relief, 56 found only partial relief, and 20 showed practically no improvement.

EXOGENOUS POISONS

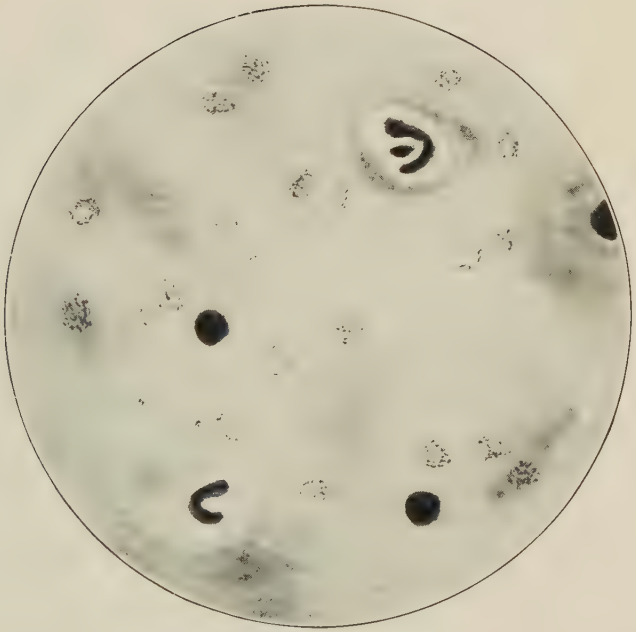
Lead Poisoning

Lead Poisoning. Diagnosis. C. P. McCord, D. K. Minster and M. Rehm[4] report what may prove to be an important means of diagnosis in lead poisoning and of measuring the precocious introduction of red cells into the circulation. The blood of healthy persons contains a few basophilic aggregations, though a variety of disease conditions having no connection with lead poisoning cause the occurrence of these aggregations; particularly conditions involving anemia. Clinical cases of lead poisoning regularly exhibit a high basophilic aggregation content of the blood. The majority of lead-exposed workers quickly come to have a higher basophilic aggregation count than is found among normal persons. This indicates a preclinical plumbism. If, in the routine physical examination of these lead workers, the basophilic aggregation count is increasing, such workers should be placed on lead-eliminating or lead-controlling treatment. We are thus, to some extent anticipating and warding off the severe clinical effects of plumbism.

The authors describe the following technic based upon the hemolysis of the red cell. As the hemoglobin is to be withdrawn and it becomes possible to see through many layers of cells they use a thick drop of blood. For staining, Manson's methylene blue is employed, which is prepared in the following manner:

(4) Jour. Amer. Med. Ass'n., May 31, 1924.

PLATE I.



Basophilic aggregations after hemolyzing staining method; blood from patient with lead poisoning; diagrammatic.—McCord, Minster and Rehm, page 308.

five gm. of borax is dissolved in 100 c.c. of boiling distilled water, to which is then added 2 gm. of methylene blue. This stain deteriorates by the end of one month. Instead of hemolyzing the blood corpuscles prior to staining, they dilute a small quantity of Manson's stain with distilled water until the stain is transparent. The unfixed slide is then stained for ten minutes. The staining is so slow under these conditions that hemolysis precedes staining. After air drying, the slides are examined microscopically, the oil-immersion lens being used. In cases of lead poisoning it is common to find 25 or more basophilic aggregations in a single field, as shown in the accompanying illustration. Preparations from the same patient, made at the same time, and stained with Wright's stain may show only a few preformed stippled cells in the entire slide. (Plate I.)

Lead Poisoning in Children. J. C. Ruddock[5] believes that pica, or parorexia, a craving for unnatural articles of food, is one of the most important etiologic factors in lead poisoning in children, and that there are many mild cases of lead poisoning in children manifested by spasms or colic the true nature of which is never suspected. The feces and the urine should be examined for lead in all children with convulsions in which the etiologic factor is not clear, and energetic prophylactic measures should be employed with children who habitually eat painted articles.

Treatment of Lead Poisoning. J. C. Aub, A. S. Minot, L. T. Fairhall, and Paul Reznikoff[6] report an experimental study on the absorption, distribution, and excretion of lead. They find that lead is absorbed more rapidly through the whole respiratory tract than through the gastro-intestinal tract. It is carried in the blood stream as a phosphate and is stored in the

(5) Jour. Amer. Med. Ass'n., May 24, 1924.
(6) Ibid., Aug. 23, 1924.

calcareous portion of the bones. Damage results only when lead is being transported after absorption or following release from the bones.

In active plumbism, lead is distributed more widely through the body than in the chronic, inactive form of the intoxication. They found that during starvation the character of chronic lead poisoning changes somewhat. Acute symptoms may develop, and at necropsy the absorbed lead is found distributed more generally through the body than is typical of the chronic condition. This suggests that during starvation, there is something unusual in the metabolism of the body which sets lead free from the bones. Acidosis seemed the most probable explanation for the change and an investigation based on this hypothesis was undertaken. It soon became evident that *if acids are given in large quantities, particularly when the calcium balance is negative, the excretion of lead increases markedly.* Of these, the most efficient is phosphoric acid, probably because it can be taken in greater quantities than hydrochloric acid, and is not burned within the body as is lactic acid. Probably the agent that most efficiently liberates lead, however, is ammonium chlorid which liberates hydrochloric acid within the body. By using it one may ingest a large quantity of acid without drinking disagreeable quantities of sour fluid. The real reason for the increased liberation of lead during acidosis is probably the fact that lead in the form deposited in the skeleton, *i. e.*, tertiary lead phosphate, is least soluble at the normal hydrogen ion concentration of the body. This salt is more easily dissolved under either more acid or more alkaline conditions. Consequently, the ingestion of acid calls on the reserve store of base in bone so that lead is liberated with calcium. Secondly, the local change in the hydrogen ion concentration of the bone renders lead more soluble. It is converted into the di-lead salt and released.

In treating patients with lead poisoning, the most satisfactory method now appears to be to give a diet with low calcium content consisting of meat, potatoes, rice, macaroni, apples, bananas, sugar, salt, milk-free bread, and butter that has been melted in hot water and skimmed off the top; to avoid absolutely milk, eggs, green vegetables, and fruits not included in this list. With this, either from 8 to 12 gm. of ammonium chlorid is given daily, or ten doses of about 20 to 25 c.c. of dilute phosphoric acid so sweetened and diluted that it tastes like lemonade. A small amount of gin added to this phosphoric acid mixture makes it much more palatable.

Sodium bicarbonate taken by patients in quantities of 40 gm. a day also increases the excretion of lead. The average increase in the excretion of lead during ingestion of acid is fourfold; during injection of alkali, about double. All these treatments do not alter the amount excreted in the urine very definitely. The increase appears in the feces.

When acid is given and the calcium balance becomes increasingly negative, the excretion of lead tends to increase progressively. When alkali is given, however, although the calcium deficiency does not increase, the excretion of lead does. In this case, lead excretion is apparently independent of calcium excretion. Repeated observation has shown that, with a high calcium intake (positive calcium balance), lead excretion tends to diminish rapidly. This provides means for controlling the storage of lead in the organism. To increase excretion it is only necessary to produce a negative calcium balance and to cause mild acidosis. On the other hand to store lead in the bones so that it will not be free in the circulation and cause damage, it is only necessary to give a diet containing much calcium in the form of milk, preventing toxic symptoms among lead workers. The milk produces a positive calcium balance, which

favors relatively harmless storage in the body. It does not, as has been generally supposed, prevent absorption of lead.

Experiments with magnesium sulphate as a cathartic have not demonstrated that it increases the excretion of lead when given alone. It does, however, relieve the spasm which appears to produce colic, for colic subsides as catharsis is established. Potassium iodid does stimulate lead excretion. Indeed, ingestion of potassium iodid causes lead to appear in the urine and the feces when they have been normal before its use; but it is not nearly as effective an agent as are the various acids.

Emery R. Hayhurst in the discussion of this paper, brought out a valuable point in the diagnosis of lead exposure. He advocates that every physician keep on his diagnostic shelf a little bottle of 10 per cent. solution of sodium sulphid, and that he take a swab and smear this on the face, arm or chest of the worker or suspected patient—best on a spot not bathed frequently and see whether the characteristic black sulphid discoloration takes place indicating the presence of lead.

Mercuric Chlorid Poisoning

Mercuric Chlorid Poisoning. H. B. Weiss[7] believes that pathologic changes take place so rapidly in mercuric chlorid poisoning that it is useless to attempt to counteract the metallic poison itself. Our efforts should be directed toward preventing the irreparable pathologic changes that will occur if the intoxication is not combated. The cloudy swelling, nephritis, and uremia are associated with an increase in the production of acid bodies. The logical treatment, then, seems to be to attempt to counteract any pathologic changes that

(7) Arch. of Int. Med., February, 1924.

have occurred; to prevent the progress of the pathologic changes; and finally, to eliminate the toxic material as soon as possible.

The treatment is divided into several stages. As soon as the patient comes under observation—the sooner the better—a stomach tube is introduced, and the stomach is washed with 2 liters of a saturated solution of sodium bicarbonate. This is continued until the washings return clear. Before the tube is removed, 180 c.c. of a saturated solution of magnesium sulphate is allowed to remain in the stomach. A soapsuds enema is then given. Most of the patients vomit soon after taking the poison, and probably some of the mercury is eliminated in this way.

To introduce alkali into the system, patients should receive an intravenous injection of alkali as soon after the preliminary treatment as possible. The preparation the author has used is Fischer's solution which consists of crystalized sodium carbonate, 10 gm., and sodium chlorid, 15 gm., both dissolved in 1,000 c.c. of distilled water. If this is not available, a solution of 4 per cent. sodium bicarbonate may be used. Patients, who have no abnormality of the circulatory system tolerate without any difficulty from 1 to 1.5 liters.

Patients who have taken large amounts of poison have been given as high as 1,800 c.c. at the first injection. The alkaline therapy is continued by mouth by a modification of the old *"potus imperialis"* by dissolving 4 gm. (1 teaspoonful) of potassium bitartrate and 2 gm. (½ teaspoonful) of sodium citrate in a glass of water, orangeade, or lemonade. The patient receives 240 c.c. of this drink from six to eight times a day, from the onset. The author has rarely used rectal administration of alkali in water on account of the irritation of the lower bowel associated with the bloody diarrhea. Hot packs have not been used except in the few patients who had a complete suppression. A liberal diet is allowed, including meat, after the diarrhea ceases.

The treatment is controlled by urinalysis. Endeavor to make the urine alkaline to methyl red, and keep it so. Fischer has demonstrated that in patients with diseases of the kidneys, the urine of whom cannot be kept alkaline to methyl red, the disease may progress and often lead to complete suppression. Under this treatment the patient usually voids large quantities of urine. Albumin, casts, and blood are usually present for several days, and gradually diminish until the urine becomes clear. Most of the patients under observation showed a normal urine from the tenth to the fourteenth day after taking the poison. If the patient has taken over 0.46 gm. of mercuric chlorid and shows marked urinary disturbance a second, and at times a third, intravenous injection of Fischer's solution is given. The injections are given on successive days. The patient usually makes a clinical recovery in from twelve to fifteen days. Examination of several of these patients a year after they were poisoned and treated did not show any abnormality that could be connected with the poisoning.

Weiss reports a series of 135 consecutive patients poisoned by some form of mercury with only eight deaths, a mortality of less than 6 per cent. These patients took from 0.09 to 3.25 gm. of mercuric chlorid. In only fifteen patients did a complete suppression develop. Of these, seven died. The patients who had the most difficulty were of the group that took over 2 gm. of mercuric chlorid, and those in whom the institution of treatment was delayed.

Alcohol

Alcohol Decreases Efficiency. In view of the prolonged discussion of whether alcohol is stimulant or depressant, the recent report of W. R. Miles* of observations on trained typists and others who received alcohol in doses of from 21 to 42 gm. in solutions of

(*) Jour. Amer. Med. Ass'n., Nov. 22, 1924.

varied strengths, including the much vaunted 2.75 per cent. beverage strength, is of interest as it gives clear cut answers.

Within the first two hours after ingestion of the smaller doses (less than 30 gm.), the pulse rate during rest and during work, the metabolism and the skin temperature show an increase. These are regularly associated with decreased reflex irritability, slower reaction, less keen senses, *i. e.*, higher sensory thresholds, slower muscular movements, less adequate and accurate muscular control, and less agile mental operations. The whole qualitative picture is one of decreased human efficiency. The factor of accuracy or adequacy of response was more prominently influenced by alcohol than was the factor of speed. Those coordinations which made a continuous demand on the subject exhibited a stronger effect than did the discontinuous type of task. In the typewriting investigation, it was discovered that with successive series of experiments on the same men, *i. e.*, the mere repetition of the routine, the alcohol influence in multiplying errors and diminishing the legibility became more pronounced. The taking of food just before or with the alcohol caused a marked decrease in the intensity of the effect.

Alcoholism. Francis J. Gerty*, Superintendent, Cook County Psychopathic Hospital, finds that practically all alcoholism now encountered clinically is of the "moonshine" type. It is a very prevalent form of poisoning at present, and in Chicago, at least, is as frequently found as alcoholism was in the pre-war and pre-prohibition periods.

The physical and mental morbidity and the mortality are high. The type of poisoning seen differs from ordinary alcohol poisoning in the following ways: the poison takes effect more rapidly, and the patient is brought to the hospital sooner because of the gravity

(*) Ill. Med. Jour., August, 1924.

of his symptoms. A smaller amount of the prevalent beverages is required to incapacitate. The effect is more profound and more often fatal. Mental deterioration is a common sequel even after a few sprees. As far as the mental symptoms are concerned, the clinical picture is usually blurred, thus making classification of cases more difficult. Pneumonia and cirrhosis have not so frequently been associated with the present form of poisoning as with alcoholism in the past. Men alcoholics outnumber the women alcoholics to a greater extent than ever.

Cyanid Poisoning

Cyanid Poisoning. W. D. McNally[8] reports six deaths following on fumigation with hydrogen cyanid. "On the night of March 3, 1923, the proprietors of a restaurant in South Chicago turned over their restaurant to a man engaged in the extermination of pests to have the roaches destroyed by him. Above this restaurant were two flats. The people in these flats were warned in a perfunctory manner by the fumigator that he was going to fumigate the restaurant below and to leave their windows open. The spaces around the water and steam pipes entering the ceiling were sealed with paper. A shaft two feet by six inches leading to the flats above was not properly sealed and the gas being generated entered the first and second flats above.

"At nine o'clock the next morning one of the owners opened the front door. The gas was so strong that he was forced to leave and was under a physician's care for two days. At 10 a. m. a roomer in the flat above who had slept in a front room with his window wide open found one of the occupants dead in the bath room. A physician was called who notified the police, who in

(8) Med. Jour. and Rec., Feb. 6, 1924.

turn found the bodies of five more people. The people in the adjoining flat and the flat above had their windows open and escaped being asphyxiated."

The use of hydrocyanic acid as an agency for disinfectation of dwellings should be forbidden by the health authorities. If its use is permitted the dangerous nature of the gas must be communicated to the owners and tenants of the building. The building must be vacated and fumigation performed by an intelligent person who understands the necessary safeguards against accident.

Botulism

Action of Botulinus Toxin. C. W. Edmunds and George F. Keiper, Jr.[9] conclude as a result of experimentation that all the essential symptoms of botulism can be explained by an incomplete curarelike paralysis of the endings of the motor nerves to the voluntary muscles, including the diaphragm, and by a more or less complete paralysis of the parasympathetic nerve endings. The paralysis of the parasympathetic is preceded by a stage of stimulation.

The administration of morphin will delay the course of the intoxication, allowing a longer time for antitoxin to exert its effects. Additional time may be secured, if necessary, by the use of artificial respiration. It is very important that antitoxin be administered as early in the course of the disease as is possible.

Anesthesia Delays Action of Botulinus Toxin. J. J. Bronfenbrenner and H. Weiss[1] find that animals suffering from botulinus poisoning placed under anesthesia may have life prolonged by a period approximately equal to that during which the administration of the anesthetic is continued. If animals are anesthetized and kept under the influence for some time, antitoxin therapy becomes effective that without anesthesia would

(9) Jour. Amer. Med. Ass'n., Aug. 16, 1924.
(1) Jour. Exper. Med., April, 1924.

have failed. Satisfactory results were obtained with phenobarbital—sodium, nitrous oxid-oxygen mixture, morphin, and ether.

Hair Dye Poisoning

Hair Dye Poisoning. In view of the fact that a solution of phenylendiamin mixed with an equal volume of hydrogen peroxid produces a deep black stain which lasts several months, this stain is commonly used to dye hair and furs. It is well known that some of these phenylendiamin dyes cause irritation and dermatitis in susceptible people. H. W. Nott[2] reports the case of the proprietor of a hair-dressing saloon who was subject to seizures for nearly three years in which, in the space of a few minutes, he would pass from a feeling of good health into a state of pain, palpitation, and exhaustion as though "he was going to die;" and on one occasion he fell on the bed helpless, certain he was dying, and lapsed into unconsciousness from which he must have passed into natural sleep, for he awoke next morning perfectly well, to find himself lying across the bed half dressed.

It was about three years ago since he first used a hair dye and occasionally applied the dye to his customers without wearing gloves, which on examination gave the reactions for both metaphenylendiamin and paraphenylendiamin.

Though bottles of this dye are issued in boxes containing notices warning people to test its effect on a small area of skin before using it, and are advised not to use it at all if a reddening of the skin results some hours after the experiment is made, the action of the dye as a systemic poison is less well known, especially as the appearance of symptoms may be delayed.

(2) British Med. Jour., Mar. 8, 1924.

It would appear from recent literature on the subject of fur dermatitis that the toxic phenylendiamin becomes nontoxic when oxidized by hydrogen peroxid. Bandrowski's base, which is formed, is an insoluble coloring matter which can be eaten by experimental animals without ill effects; but apparently the phenylendiamin is not always completely oxidized, and to prevent the furs remaining toxic they are washed for from seven to eight hours. It is only when the washing has been scamped that the furs are toxic and cause dermatitis.

A similar process is used in hair dyeing; the hydrogen peroxid and the phenylendiamin are mixed, and the resulting solution is applied to the hair, but unfortunately a temptation exists not to wash too thoroughly as the washing may spoil the color. Still worse, some who do the dyeing themselves, apply the solutions separately, by which means they obtain a finer and more lasting color, but probably run greater risk of a toxic result.

If careless men dye heavy moustaches in this manner, and women with similarly dyed hair hold tresses of it between their lips while dressing, the possibility of poisoning is increased. So long, therefore, as people are willing to use this dye in quantity, elderly-looking people with suspiciously dark brown hair may occasionally be met with whose paroxysmal tachycardia or indigestion, whose palpitation or liverishness, or whose symptoms of gastric influenza will disappear if they will stop dyeing their hair.

DRUG ADDICTION

In General

Drug Addiction. W. H. Willcox[3] insists that we regard inebriety as a disease rather than a wilful vice, and that alcoholism and drunkenness are only one variety of the disease "inebriety." To avoid confusion

(3) British Med. Jour., Dec. 1, 1923.

he suggests as an alternative term for inebriety "narcomania," an overpowering impulse for narcotism by any intoxicating or anesthetic substance.

It is impossible to name with limitation the drugs which may give rise to an addiction habit, because any drug having an intoxicating action on the cerebrum may give rise to addiction, besides new drugs of organic composition are being daily added to our pharmacologic armamentarium, the effect of which as regards addiction is at present unknown. It should be more generally recognized that there are many other drugs of addiction besides morphin, cocain, and alcohol. The group barbital, medinal, proponal, dial, and phenobarbital, are all dangerous from the liability to addiction. Their continued use leads to the development of a definite symptom-complex such as an abnormal mental condition, in which delusions and visual hallucinations may occur. The speech may become thick and indistinct and visual disturbances appear. The gait often becomes ataxic. The barbital habit leads to a disorganization of the moral sense. A common sequel of addiction to it is suicide, usually by means of an extra large dose.

None of the drugs in this group should be obtainable except on medical prescription. Cannabis Indica, sulphonal and its homologues, trional and tetronal, paraldehyde, ether, chloral, and chloroform should all be obtainable only on medical prescription.

Dionin has only feeble powers in the causation of addiction, though a few isolated cases are recorded. It has been used in the treatment of morphin addiction, and is of some value in warding off withdrawal symptoms. It is not included among the dangerous drugs.

Codein is not really dangerous as an addiction drug, and has (in England) been wisely excluded from those in the Dangerous Drugs Act.

The hypodermic use of morphin, heroin, or cocain is to be avoided as far as possible. Other methods of treatment are usually available, such as local treatment

by radiant heat, diathermy, or other electrical treatment, or by external anodyne applications. Many analgesic drugs, such as phenacetin, pyramidon, aspirin, are of use. Where a particular nerve is involved, alcohol injections are invaluable. The hypodermic injection of addiction drugs should be a last recort only. How easy it is to relieve the pain by the injection of a small dose of heroin or morphin, and how quickly does the repetition of the dose become necessary!

In acute conditions it may be necessary to procure sleep at all costs, and for this purpose there is no surer method than the administration of morphin or heroin hypodermically. Repetition is to be avoided. The terrors of insomnia are not to be compared with those of drug addiction, and a little sleep following natural methods of treatment is of far greater benefit than the more prolonged abnormal condition of sleep produced by narcotic drugs.

The danger of addiction is very much greater in patients with a neuropathic temperament than in others. Often a psychological complex of a depressing type is present in patients of this group and there is a subconscious cry for relief from mental suffering. Persons of this type are out of harmony with their environment. They constantly call for something to "drown the cares of life." This relief is temporarily obtained by the administration of a narcotic drug, and as surely as this occurs so inevitably does a still deeper stage of mental agony develop, which is only to be relieved by the further resort to the narcotic.

That one drug habit leads to another is an axiom which may be laid down for almost all cases. Thus the morphin addict frequently resorts to cocain or alcohol as alternative measures of relief for his states of mental depression. Indeed, in some cases the craving for drugs of any kind available becomes almost an obsession. In cases of drug addiction of long standing it is frequently

found that a combination of drugs is used, morphin or heroin with cocain or alcohol being the commonest combination.

Association with addicts is one of the commonest causes of addiction. The addict desires nothing so much as leading astray the innocent. The pleasures following the dope are painted in most glowing colors and the neophyte is besought to partake of them. In some cases, especially among women of the underworld, cocain and heroin are taken commonly as snuff with the idea that transitory mental brilliance and attractiveness are produced. Prostitution and sexual vice are closely associated with drug addiction. Cocain may in early stages of addiction have an erotic effect, and there is evidence that it is an important factor in the causation of unnatural sexual vice.

Ambulatory treatment of drug addiction almost always fails and should not be attempted. There is no panacea for the cure of drug addiction and the much vaunted "cures" and "patent medicines" are usually worthless and do more harm than good. The only treatment that gives prospect of complete cure is one which recognizes that drug addiction is a disease, and as such requires the same careful attention to detail that any other disease (typhoid fever, pneumonia, etc.) would receive. Thus the general standard of health should be raised to as high a pitch as possible, any associated toxic or other predisposing factors should be dealt with, and the withdrawal effected under the most favorable conditions both physical and psychic. Treatment in an institution or nursing home with complete supervision is essential.

Where the general health of the patient is good and where the addiction is of short duration sudden withdrawal is advisable. In cases of addiction of long duration, especially if the general physical condition is low gradual reduction is advisable. In cases of this type hyoscin has been advocated, a mild hyoscin delirium

being produced for 36 to 48 hours by repeated small doses given hypodermically. At the end of this no morphin is given. The author doubts whether any ultimate advantage is gained from hyoscin treatment.

After withdrawal has been effected the after-treatment is very important, and in this stage, in addition to general hygienic and medicinal methods, psychotherapeutic treatment is most valuable. The cultivation of the will power and of a feeling of hopefulness and certainty of recovery are most important factors for success in this phase of the treatment. Focal sepsis must always be carefully looked for in cases of drug addiction, and one of the first elements of treatment should be the removal of septic absorption from such causes.

Barbital

Barbital Intoxication. Irving J. Sands[4] states that the amount of the drug ordinarily causing acute toxic symptoms is above 3.25 gm. Patients having taken amounts from 3.25 to 8 gm. have made good recoveries. Recovery from more than 8 gm. is not common. In acute intoxication, the patient is usually comatose; the temperature may be sub-normal, or moderately elevated; the pulse is either very slow or rapid; respiration may be lowered or increased. The face is flushed, the lips and finger tips are somewhat cyanosed, and the extremities are cold and clammy. The blood pressure is low. The urine in this state is diminished in quantity, of specific gravity somewhat higher than normal, and contains traces of albumin and granular and epithelial casts. The drug may be recovered from the urine. The tongue is heavily coated and the breath is foul. The bowels are constipated. Usually there is incontinence of urine and feces. The corneal and abdominal reflexes may be absent. The knee jerks are diminished, and in severe cases are often absent. The pupils may not react

(4) Jour. Amer. Med. Ass'n., Nov. 3, 1923.

to light. Spontaneous contraction and dilatation of the pupils are often encountered, and this phenomenon is regarded by some authorities as being pathogmonic of the condition. Ptosis and diplopia may be present. Amaurosis has been reported. Nystagmus is frequently encountered. The coma may last from 24 to 72 hours, and the patient may gradually regain consciousness. He then invariably will show ataxia, dyssynergia, a thick, drawling, indistinct speech, and he may complain of diplopia. Often a stage of delirium may supervene of the usual occupation delirium type. After consciousness is regained, the patient is irritable and at times ugly making unusual demands from the nurses and physicians. Recovery may be complete in from two to three weeks. The danger signs in the acute period are the absent abdominal and knee reflexes, and brochopneumonic conditions.

In cases of chronic intoxication, the patient presents a general cyanotic appearance, possibly with erythematous skin lesions. The gait is ataxic, the station is unsteady, and there is a general dyssynergia. The speech is drawling and indistinct. Frequently there is omission of letters and syllables. The breath is foul, the tongue coated, and constipation persistent. The temperature is somewhat subnormal, the blood pressure is low, and the pulse slowed. The outline of the pupils may be normal, or may show inequality and irregularity. Reflex disturbances may be present. There is often a defect in attention, retention, and association. Memory, especially for recent events, is poor. Emotional instability is common, and frequent outbursts of temper are encountered. The patients never have a clear insight into their own condition and their judgment is faulty. They often complain of insomnia and of general restlessness. They may become quite deluded, and may blame others for their failure of adaptation. Unless there is a defi-

nite history of taking barbital, diagnosis of the conditions is not always easy. The condition may simulate epidemic encephalitis or uremic coma. Even brain tumor and pneumonia have been considered diagnostic possibilities.

Sands' own experience leads him to believe that the vast majority of patients suffering from acute veronal intoxication belong to the manicdepressive group, while the largest number of chronic barbital patients belong to the emotionally unstable type of constitutional psychopathic inferiority group. Acute intoxication usually results from taking a large dose of the drug while in a state of extreme depression, occasionally with suicidal intent. Chronic barbital addiction results from repeated taking of the drug by an emotionally unstable person in his inability to face reality because of the painful effect it might entail.

In the management of these cases it is important that the drug be eliminated as rapidly as possible. High colonic irrigation, catheterization, and warm packs have proved valuable. Cardiac stimulants and oxygen inhalation have been found very useful in the more serious cases. The patient must be kept warm. Pulmonary complications must be anticipated and energetically combated.

The restriction of the sale of the drug on physicians' prescriptions only, and the use of its proper chemical term, diethylbarbituric acid, would materially diminish the number of poisoning cases.

SACCHARIN

Saccharin Harmless. In a court proceeding, instituted in the Federal Court at St. Louis in 1919, by the United States Government against the Monsanto Chemical Works of St. Louis, Missouri, manufacturers of saccharin, it was contended by the Government that the

manufacturers were guilty under the Pure Food and Drugs Act of misbranding, because the label on their saccharin package contained the words "absolutely harmless." Expert testimony was presented by the Government to prove its contention that saccharin is not absolutely harmless. At the conclusion of the trial, the jury, after long deliberation, remained disagreed and was discharged as "a hung jury." Again, during the latter part of April, 1924, the Government brought identical suit against the Monsanto Chemical Works, at the end of which trial lasting more than a week, the jury was once more disagreed and was discharged—"a hung jury."

So positive and so persistent were the attorneys for the Government in their contention before the jury that it was determined by a group of five of the witnesses for the Chemical Works, David L. Penny, Charles L. Klenk, Scott Heuer, Harry G. Bristow and Leon L. Solomon,* to perform experiments on normal, healthy male adults, in order to determine what effect, if any, saccharin might have on secretion and digestion in the mouth and in the stomach, on intestinal absorption and on kidney elimination. Their conclusions are that salivary secretion and salivary digestion are not inhibited. The quantity of appetite gastric juice is not decreased. The amount of free acid and the total acidity show no significant difference. There is no difference in the digestive action of the appetite, gastric juice, or the quantity, the acidity, or the digestive activity of the gastric juice. It does not decrease absorption from the intestine, and does not affect elimination from the kidney.

[Have carried on experiments in which rats were fed several times their weight in saccharin in the course of months without being able to produce evidence of harm done by the saccharin.—Ed.]

(*) Med. Times, September, 1924.

ANTIDOTES AND ANTAGONISTS

Thiosulphate

Sodium Thiosulphate as an Antidote for Arsenic, Bismuth, and Mercury Poisoning. Henry C. Semon[5] reports a series of cases of metal poisoning beneficially treated by intravenous injections of sterile solutions of chemically pure sodium thiosulphate in doses of 0.45, 0.6, 0.75, and 0.9 gram. He believes that in sodium thiosulphate we have a specific, safe and rapid antidote for stomatitis due to mercury and bismuth; and that it also offers a hope that the course of arsenical poisoning both in the skin and the liver, can be controlled and in some degree shortened by its administration.

The action of the salt when injected into the circulation containing a metal or an arsenical derivative is an interesting biochemical problem. The author finds it difficult to accept the theory that an insoluble sulphid is formed. Whatever the chemistry, there is no doubt that the distressing symptoms of mercurial and bismuth stomatitis are effectively and rapidly relieved. Three to four injections of 0.45 to 0.6 gram, given intravenously in 5 c.c. of water on alternative days were found sufficient (in four mild cases) to clear up the fetor and salivation and permit of early dental treatment to insure against a recurrence.

The author also cites a case that seems to demonstrate local antidotal properties of thiosulphate. During the injection of 0.6 gram of novarsenobillon in 10 c.c. of water the needle slipped through the posterior wall of the vein and the last part of the barrel contents (about 2 c.c.) formed a distinct tumescence subcutaneously. The patient complained of severe burning pain and fainted. The syringe was disconnected, leaving the needle *in situ*, and 8 c.c. of distilled water, containing 0.75 gram of sodium thiosulphate, were injected so as to mix with and dilute the novarsenobillon solution. A week later there

(5) British Med. Jour., Apr. 12, 1924.

was no trace of local infiltration and apparently no pain, on deep pressure over the site of the injections which was still marked by the presence of a bruise where blood had escaped from the perforated vein. This is the first time in the author's clinic than an extravenous leak of novarsenobillon has escaped the sequela of painful subcutaneous infiltration.

Thiosulphate in Post-Arsphenamin Eruptions. Hiram E. Miller[6] believes that sodium thiosulphate should be used in all cases of arsphenamin dermatitis that fail to improve under local treatment after a period of a week or ten days. He thinks it advisable to wait this length of time in view of the fact that a large percentage of the cases will clear spontaneously. Though no toxic or disagreeable symptoms due to the drug have been experienced, unnecessary intravenous therapy of any kind should be avoided as much as possible. The technic of administration is that of neo-arsphenamin. The drug for intravenous use must be pure and must be sterile. It has been put on the market by the H. A. Metz Laboratories in air-tight, sterile ampules, similar to arsphenamin. In general, the injections are given at 24 hour intervals for the first four smaller doses, and at 48 hour intervals for the two to four succeeding larger doses. The dosage is 0.3, 0.45, 0.6, 0.9, 1.2 and 1.9 grams respectively. It is given intravenously by the syringe method dissolved in ten to twenty c.c. of sterile distilled water. This is supplemented by one gram of the drug given orally three times a day, dissolved in water. One course of treatment consisting of six to eight injections will generally accomplish as much as can be expected from the drug. Many of the patients will have a few areas of dermatitis remaining after the completion of the course of sodium thiosulphate. These are generally in the distribution of a seborrheic dermatitis and clear in a few weeks with the use of local mild antiseborrheic remedies.

(6) California State Jour. of Med., November, 1923.

In 1920, Revaut of France described the use of this drug orally and intravenously in the treatment of arsenical dermatitis. His theory is that sodium thiosulphate converts the metal arsenic into nontoxic insoluble sulphides which are in time eliminated from the body. Whether this is what actually happens in the body is difficult to say. [Very improbable.—Ed.] The interesting observation is that it greatly shortens the course of the eruptions.

Practically all of these patients remain intolerant of the drug for months or years after their arsphenamin eruptions. In the severe cases the danger of a recurrence of the dermatitis is such a serious one that it is advisable to continue the treatment with mercury and iodids. In the milder cases, if arsphenamin is to be used it should be used cautiously. Intradermal tests with a small quantity of arsphenamin solution will generally tell if the patient still has an idiosyncracy to the drug. Treatment with mercury and iodid should not be started until all areas of dermatitis have entirely cleared.

Caffein

Caffein as Antagonist for Morphin. Charles C. Haskell, J. E. Rucker, and W. S. Snyder[7], as a result of experiments performed on cats, find that caffein either in large amounts or in doses quite comparable to those sometimes employed clinically instead of proving an effective antidote for morphin poisoning actually exerts an unfavorable action. This is in harmony with the results of Hale and of Pilcher, the former finding that caffein lessened the chances of recovery from severe ethyl alcohol poisoning. It is suggested that the undesired synergism is exerted on the heart. That a deleterious action would result from the use of caffein in a human being suffering from morphin poisoning cannot be stated positively. Quantitively, there is a vast difference in the

(7) Arch. Int. Med., Mar. 19, 1924.

action of morphin on man and on any of the animals used in this investigation. It is possible that the respiratory center of man is peculiarly sensitive to the action of morphin, so that death in human beings would result from doses of morphin which affect the circulation little or not at all; while, on the other hand, in the lower animals, the larger doses necessary to cause death involve the heart muscle also. If this is the case, it is conceivable that caffein, by combating the respiratory depression which is the chief or sole factor in clinical morphin poisoning, may be of value as a physiologic antidote. It is generally assumed that morphin is practically free from a depressant action on the circulation when used clinically.

PHYSICAL AGENTS
ELECTROTHERAPY

Electrophoresis. George T. Pack, Frank P. Underhill, Joseph Epstein and I. Newton Kugelmass[8] arrive at the following conclusions as a result of their experimental studies:

I. The electric current may be used as a means of driving ions into the skin. In the case of the heavy metals, as Hg**, Mg**, Zn**, Pb**, their ions as soon as they enter the skin give up their electrical charge to other much faster traveling ions present in the tissues, *e.g.,* H, and Na. The metals then losing their charges enter into combination with the protein and salts of the tissues, and may form precipitates. These are redissolved too slowly to be demonstrable by the common chemical tests in the excretions. *Heavy metals, therefore, may be efficient for purely local administration, but not for systemic effect.*

II. The electric current facilitates the introduction of many alkaloids through the skin. Systemic effects of strychnin and pilocarpin were demonstrated upon rab-

(8) Amer. Jour. of Med. Sci., May, 1924.

bits after electrolytic administration of the drugs for approximately one hour each. Controls without the current were negative. The action of caffein and curare failed to be demonstrated upon rabbits after electrolytic administration of the respective drugs for approximately two hours each. The action of curare, picrotoxin, strychnin, veratrin and nicotin was shown to be definitely accelerated when electrolytically introduced into frogs' skin, as compared with controls. Experiments with local anesthetics in which a current of 2 ma. was used for ten minutes upon a human subject showed that:

1. Cocain produced moderate but incomplete anesthesia of finger lasting about one hour.

2. Procain and butyn produced mild anesthesia lasting about one-half hour.

3. Benzylcarbinol and salicain failed to produce any significant anesthesia.

III. Halogens, non-metals, and acids, being anions are introduced by anaphoresis. The ingress of some is demonstrably accelerated by the electric current (CN, I_2), while in others there could not be demonstrated any acceleration of introduction by the electric current (NO_2, salicylates).

IV. The theory of detoxication of poisonous ions by electrolysis is fallacious. The application of an electric current is not specific for the egress of particular ions except those with a relatively great migrational velocity (*i.e.*, H, Na, Cl_2, I_2). The migrational velocity of the ions of the common poisons, as the heavy metals and alkaloids, is very small as compared to that of the ions normally present in the tissue, and therefore the principle of detoxication cannot be applied to the former.

V. After the administration of iodids, per os or subcutaneously, nascent iodin can be liberated within the tissues by the insertion of a positive pole of an electrode. This principle may possibly be utilized in the treatments of certain infections. However, equally beneficial effects

seem to be obtainable by the application of the electric current *per se* as a result of the drastic tissue changes which are produced. These phenomena are: the formation of heat, the release of nascent oxygen, the production of concentrated acid, and the bacteriotropic influence of the positive pole for the negatively charged protoplasm of the staphylococci. The authors' results tend to validate the rationality of Fowler's (1913) employment of the electrolytic bath in the treatment of septic wounds. He immerses the wound in a warm solution of NaCl and places the positive electrode in the bath. The stimulation of tissue regeneration and epithelial proliferation by the galvanic current is another modifying factor.

Electricity in Dermatology. As an antidote to the flamboyant literature of the manufacturing houses of physical therapy apparatus, the report of Ernest Dwight Chipman[9] might be very serviceable. The author cites two cases in which the galvanic current seemed useful for stimulation of the nutrition of the scalp. Zinc ionization has been used successfully in the treatment of lupus erythematosus. Electrolysis is the treatment *par excellence* for superfluous hair. Our selection of cases should, however, be judicious. We must resist all entreaties from those who insist on the removal of down. Above all, we must be firm with those who have heard of the magic of the roentgen rays but have never seen the damage that has resulted from their improper use.

Though there are several other conditions in which electrolysis may be used with excellent results, particularly in non elevated nevi, the author uses the galvanocautery even for such lesions as spider nevi and sometimes for the dilated capillaries of rosacea. In dealing with these fine capillary lesions a very delicate cautery tip is essential. It is formed by drawing a fine strand of platinum wire into a loop with the two sides of the loop so closely parallel that it presents more nearly the

(9) Jour. Amer. Med. Ass'n., Sep. 27, 1924.

appearance of a needle. In the case of hairy nevi, the needle is preferable, although, in certain cases, it may be used in conjunction with the galvanocautery. If there are only two or three hairs they may be destroyed individually by the needle leaving the remainder of the mole to be treated with the galvanocautery. This insures the finest cosmetic result. In the treatment of the enlarged capillaries seen in rosacea, the author had most satisfactory results with the cautery.

In no single condition has treatment with the galvanocautery been more gratifying than in xanthelasma, In granuloma pyogenicum both the galvanocautery and roentgen rays are effective. In molluscum contagiosum, the galvanocautery speedily ends the trouble. For a great variety of benign new growths, this treatment is simple and effective. In small pedunculated tumors, the use of a tip shaped like a knife blade makes bloodless surgery. Even in the small nonpedunculated lesions the blade may be applied in short successive strokes around the circumference and the growth removed with practically no resultant scar. Cutaneous horns and certain kerotoses are most effectively treated with this agent, and it has been used successfully in lupus vulgaris, cancer, and rhinophyma.

In the treatment of small growths, the question of using a local anesthetic sometimes arises. Properly performed, the ordinary operation causes no more pain than would result from the punctures of the hypodermic needle. Occasionally some procain is clearly called for, but it is surprising how easily the cautery is tolerated if only the operator takes the time to proceed slowly with many short contacts instead of attempting to finish the work in a moment.

As a possible disadvantage should be mentioned the remote chance that hypertrophic scars may result. For this reason it would seem advisable, if one contemplates the removal of multiple lesions especially on the face, first to test the possibility of such complication by oper-

ating on a single lesion in order to observe the result before undertaking the treatment of the remaining lesions.

The field of ultraviolet rays is limited. In generating ultraviolet rays two types of lamps are used, the air cooled quartz mercury vapor lamp and the water cooled quartz mercury lamp. The former is commonly known as the Alpine and the latter as the Kromayer lamp. It would seem that the air cooled lamp is of service in the more superficial lesions while the water cooled lamp is to be preferred in deeper seated affections. Thus, the Alpine lamp has been remarkably effective in parapsorasis. In psoriasis it has been of help in some cases but, on the whole, it is not to be compared with either the roentgen ray or even chrysarobin. In certain squamous eczemas, it has given satisfaction. In pityriasis rosea it has been of distinct service. In alopecia areata it has not given results that were appreciably better than with other forms of electrical treatment or a good chemical stimulant. In acne it is necessary to use the ultraviolet rays to the extent of securing desquamation, but most would prefer the imperceptible and painless method with resorcinol. The Kromayer lamp is especially useful in lupus erythematosus, port wine marks and angioma serpiginosum. In tuberculosis of the skin as good or better results may be obtained with the roentgen ray.

The author has not much use for the high frequency current. Treatment by fulguration, while notably successful in certain hands, has never appealed to Chipman since in most cases the same results seem to be obtainable with less pain and more certainty with the use of the galvanocautery and the roentgen rays. The use of the high frequency current with glass electrodes is declining for the reason that nothing is accomplished thereby that is not more easily or expeditiously effected by other methods.

DIATHERMY

Diathermy of Limited Value in Internal Medicine. Edward W. Jackson[1] reports the results obtained from 1,470 applications of diathermy to 61 patients suffering from various conditions common in internal medicine. He concludes that diathermy is of value *for the reduction of arterial hypertension,* but *sedative baths under carefully prescribed conditions are equally helpful.* Diathermy has given symptomatic relief in many painful conditions more promptly than has been obtained under usual treatment. Jackson considers it an addition to our other therapeutic resources.

In the reduction of arterial hypertension by office treatment his results were practically *nil,* unless rest followed the treatment. Under ideal conditions, to reduce hypertension, the patient should rest in bed for several hours directly after the treatment. The retention of the heat in the body tissues would thus be aided and its physiologic action prolonged and augmented. It is obvious that such conditions can be attained only when patients are staying in a properly equipped hospital or sanatorium, or by treatments given in the patient's home.

Though with careful attention to details, diathermy reduces arterial hypertension, and as long as the treatments are continued, keep the pressures within safer limits, the treatments were so time consuming and harassing to the patients and physician that it was with a feeling of relief he entered into an agreement with eight of these patients to compare the action of baths with that of diathermy in reducing their pressures.

Directions for these baths were as follows: "The bathroom must be warm and everything in readiness so that one may retire immediately following the bath. Fill the tub with water and maintain it at a temperature between 98 and 102 F. as determined by a reliable

(1) Jour. Amer. Med. Ass'n., July 26, 1924.

bath thermometer. Lie comfortably in the tub, fully relaxed, for from fifteen to 30 minutes, or until drops of perspiration are felt gathering on the forehead. No attempt must be made to dry thoroughly, the drip only being wiped away. Put on outing flannel night-clothing and drink ½ glass of hot water before retiring. Should you feel faint or weak stop the bath at once and retire."

The effects of such a bath under the prescribed conditions followed by nocturnal bed rest for from eight to twelve hours are superior to other methods of hydrotherapy in the treatment of hypertension. Invariably a reduction of pressures follows these baths which compared favorably with that secured by diathermy. Restlessness, insomnia, and weakness followed overtreatment as with diathermy and it was necessary to adjust the frequency and duration of the baths and to caution that the proper temperature of the water be observed. There is a minimum to which any given case of compensatory hypertension may be reduced without provoking symptoms and signs of circulatory failure. This point should be established by a few weeks of intelligent observations and treatments and efforts should then be directed toward maintaining the pressure at this optimum level. As long as the fall of the pressures is unaccompanied by circulatory or nervous discomfort, whatever the method used it is safe to proceed cautiously with attempts to lower them. Baths and diathermy, singly or when wisely combined and adjusted to fit the particular patient, are equally efficient in reducing hypertension. This reduction persists as long as the treatments are continued, provided the other important factors—rest, diet, and hygiene—are faithfully observed. When baths and diathermy are stopped or indifferently given the pressures gradually creep up.

Five patients with organic angina pectoris believe that diathermy has been of definite value to them, their attacks being less frequent and severe. Precordial pains

to the left of the sternum were also relieved by diathermy. Pains lacking the predominating complaints of organic angina pectoris namely, attacks characterized by substernal pain associated with fear of death, should be regarded with skepticism as indicating true angina pectoris whether or not there is evidence of organic cardiac disease. Pains to the left of the sternum are, in his experience, commonly associated with focal injection. Definite intercostal neuralgia and myalgia are frequently encountered both with and without a discoverable source of infection. If complete relief is not obtained from diathermy a source of infection must be located and removed.

Diathermy in Urology. H. W. E. Walther and C. L. Peacock[2], on the basis of experience with 73 urologic cases, believe that diathermy as employed with the newer type of apparatus is an agent whose potentialities for goods have been but half developed.

For treating primary papilloma of the bladder surgical diathermy has no equal and it offers as much relief to malignant conditions in this viscus as any other one agent. Tumors of the urethra in the male can be treated as expeditiously with surgical diathermy through the cysto-urethroscope as can tumors of the bladder through a cystoscope. They feel that tumors of the meatus urinarius and urethra in the female are being overlooked far too frequently by physicians. Among the factors producing symptoms of "bladder trouble" in women, they would place papilloma of the urethra among the most common. A good urethral speculum or a skeneoscope will aid materially in bringing them to light. Diathermy has been found, in the authors' hands, superior to any other mode of destroying these excrescences promptly and permanently.

Diathermy is specific for chancroid. In granuloma inguinale, it destroys the local process with more dis-

(2) Jour. Amer. Med. Ass'n., Oct. 11, 1924.

patch by far than when antimony and potassium tartrate alone is used. In suppurative inguinal adenitis complicating lesions of the external genitals, the employment of surgical diathermy to sterilize more efficiently the evacuated pocket has proved a decided advantage over the use of antiseptic solutions.

In three cases of endocervicitis the results have been so encouraging that the authors venture to predict that diathermy will soon occupy the position *par excellence* in the therapy of gonococcal endocervicitis.

Of the many treatments that have been advanced for epididymitis, sedative diathermy has proved the most satisfactory. The instant relief of pain, the more rapid subsidence of swelling, and the ability of the patient to return to his duties more promptly are among the advantages that can be credited to the procedure. For a patient who has presented himself suffering excruciating pain to be placed on a table and given twenty minutes of sedative diathermy and then walk off in comfort is common experience. He is instructed to rest in bed for a day or so and then return for observation. If relief has been constant, he may return to work provided it is not too strenuous. One treatment suffices for the majority of cases. Two or three applications were found necessary in a few instances. In the treatment of prostatitis and seminal vesiculitis the authors failed to get uniform results with sedative diathermy. They believe the results might have been better with the use of a machine of higher voltage. For detailed description of the technic the reader must be referred to the original article.

RADIUM THERAPY

Radium Emanation Therapy. Frank Edward Simpson[3] enumerates the advantages of radium emanation over radium itself as follows: First, the danger of

(3) Illinois Med. Jour., November, 1923.

losing the radium is obviated. Second, it is possible to concentrate a very large dose in a very small tube. In the larynx, for example, one may use 600 or 800 or more millicuries in giving an exposure for intra-laryngeal cancer. It would be impossible to introduce this quantity of radium itself into the larynx. Third, in suitable cases, radium emanation contained in minute glass ampules can be inserted directly into the tumor tissue. This newer method has practically revolutionized the treatment of certain tumors and has rendered the use of steel needles containing radium salts for the puncture of tumors practically obsolete. In using the intra-tumoral method the most minute doses are sufficient, and indeed, large doses may be actually harmful. It is not advisable to use over ½ to 1 millicurie of emanation in each ampule. On the other hand, in employing surface or "distance" radiations, very large quantities of radium are advisable and even necessary if the best results are to be obtained. To obtain the best effects, at least 1,000 millicuries of emanation must be available. Too small quantities of radium, an insufficient equipment and an incorrect technic are responsible for some of the present unpopularity of radium treatment in certain quarters.

Radium rays are approximately four times as penetrating as the hardest roentgen rays that can be technically produced. If an adequate supply of radium is to be had and if the technic is correct even more intense deep effects can be produced with radium than with roentgen rays because of the greater penetrating power of the gamma rays. In dealing with selected cases of localized tumors every part of which can be reached by means of a needle the puncture of such tumors for the purpose of introducing glass emanation ampules is effective. In dealing with tumors which are very diffi-

cult of access the method of "distance" raying with upwards of a gram of radium element may be chosen. Sometimes a combination of these two methods is most effectual.

ROENTGEN THERAPY

The Nature of Roentgen Rays. John K. Robertson[4] gives us the reason why these rays should no longer be called *x*-rays. For many years after their discovery, the exact nature of the rays was a subject about which there was much speculation. Until 1912 there was ample justification for naming them by the third last letter in the alphabet. In that year, however, it was experimentally demonstrated that the phenomenon of interference could be obtained with *x*-rays and that consequently they were a form of wave-motion.

Because of the extreme shortness of both visible and invisible light waves, another unit of length needs be used for convenience in discussion. This new unit, which is called the Angstrom, is simply 10^8 cm., that is, one hundred-millionth of a centimeter. Thus, instead of writing 0.00006 cm., we write 6000 angstroms or 6000 A.U. The range of wave-lengths used in radiology extends from 0.3 A.U. to 0.06 A. U. Table I gives a summary of all classes of ether waves with approximate limits, while (Figure 17) shows graphically (logarithmic scale) the complete range. It should be clearly understood that, although one class is called electrical, all these waves are of the same character, all electromagnetic. Differences in their properties correspond solely to differences in their wave-lengths.

(4) Jour. Radiology, November, 1923.

TABLE I

	Range of Wave Lengths
Electrical	10^3 cm. to 0.08 cm.
Infra-red	0.031 cm. to 0.00007 cm.
Visible	0.00007 cm. — 0.00004 cm.
	7000 A.U. — 4000 A.U.
Ultraviolet in Therapy	4000 A.U. — 2000 A.U.
Extreme Ultraviolet	4000 A.U. — 200 A.U.
X-Rays	500 A.U. — 0.06 A.U.
X-Rays in Radiology	0.3 A.U. — 0.06 A.U.
Gamma Rays of Radium	1.4 A.U. — 0.01 A.U.

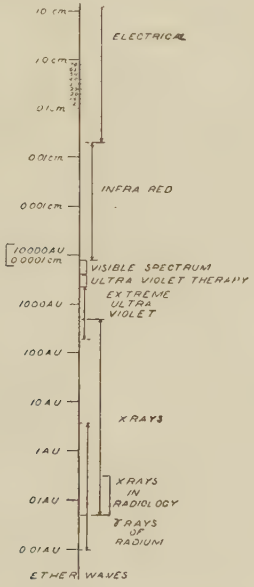


Fig. 17.—Complete logarithmic scale of electro-magnetic waves. The difference in their properties depends upon differences in their wave-lengths.

Intestinal Ulceration Produced by Roentgen Rays. S. L. Warren and G. H. Whipple[5], continuing their work on intestinal lesions and acute intoxication produced by radiation in dogs and extending it to a variety of other animals, show that the common labora-

(5) Jour. Exp. Med., Dec. 1, 1923.

tory animals are about equally sensitive to the *x*-ray given over the abdomen. The clinical reaction following a M. L. D. is very similar and the intestinal pathology almost identical. By contrast, birds, frogs, and reptiles are very resistant to the *x*-ray and may tolerate two or three doses of radiation lethal for dogs. These data strengthen their belief that the human intestinal tract is likewise sensitive to radiation. This fact must be given careful consideration in conditions where abdominal or pelvic radiation is being used because such injury done to intestinal epithelium is always serious and in some cases irreparable.

A single large dose of *x*-rays over the abdomen will cause a definite injury of the mucosa of the small intestine and the severity of the clinical intoxication seems to parallel this recognizable epithelial injury. This clinical intoxication lasts four to six days if the *x*-ray dose is sublethal. Subsequent doses of radiation given within this period of clinical intoxication give recognizable evidence of summation or a cumulative effect. Doses of radiation given at six days, or longer intervals, show no evidence of summation. The reaction of this relatively sensitive intestinal epithelium to radiation may be similar to the reaction of certain deep lying tumor tissues to *x*-ray therapy and the experiments may give information of value to physicians concerned with *x*-ray or radium therapy.

X-rays which injure intestinal epithelium (and presumably other body or tumor cells) travel in straight lines from the target through the living tissues, forming a cone or beam of rays as controlled by impervious screens. Lesions in the stomach and intestine may be confidently predicted from a knowledge of the size and form of the cone or beam of *x*-rays given over the abdomen. These lesions, even more than skin burns do not heal, and may in fact go on after many weeks to perforation. Even in the depths of the abdomen the duodenal lesions are as clean-cut as a peptic ulcer,

indicating the lack of dispersion or scattering of the primary or secondary rays in passage through the living tissues.

These experiments show the erroneousness of the belief accepted by physiologists, bacteriologists, and pathologists alike that the covering mucosal epithelium of the intestinal tract is a very important, if not the all important, barrier which guards the underlying tissues, lymph, and blood vessels from overwhelming invasion by hordes of bacteria that swarm in the intestinal tract. This barrier may be wiped away completely and yet the expected overwhelming invasion does not follow. Evidently the other tissues or the tissue juices have a protective mechanism, perhaps a form of secondary defense which is of much importance and is not to be neglected in estimating the resistance of the intestine to bacterial invasion.

The authors[6] conclude that the evidence from animal experiments and scattered clinical observations is convincing that the human intestinal mucosa is peculiarly sensitive to the hard and short wave length roentgen rays. It is probable that the intestinal epithelium is at least as senstitive as the skin epithelium, and it may be more sensitive. Erythema doses or larger doses given over the abdomen or the intestinal areas may cause injury to this sensitive intestinal epithelium. Hence, particular care should be taken when "cross fire" is used over areas that include intestinal coils, as the loops may be seriously injured. Local roentgen ray injury to intestinal coils may not give rise to severe clinical intoxication, but may cause ulcers that are no less chronic and dangerous than are the familiar roentgen ray skin "burns."

Effect of Roentgen Rays on Gastric Secretion. A. C. Ivy, J. E. McCarthy, and B. H. Orndoff[7] find that exposure of the thorax of Pawlow pouch dogs to roentgen rays sufficient to cause a first degree burn has no

(6) Jour. Amer. Med. Ass'n., Nov. 17, 1923.
(7) Ibid., Dec. 20, 1924.

effect on gastric secretion and causes no symptoms. A similar dose delivered over the lower abdomen causes a temporary anacidity or hyponormal secretion associated with anorexia followed by a return to normal of gastric secretion and appetite with a progressive loss of weight and cachexia. Necropsy shows chronic ulcers of the intestine. A human erythema dose of roentgen rays of short wave length delivered over the abdomen causes a hypernormal secretion of gastric juice lasting one or two days, followed by anorexia, hyponormal secretion, and sometimes diarrhea, and followed on the fifth day by normal gastric secretion and appetite. This dose causes death in from six to fourteen days in dogs that are not in perfect condition. Seventy-five per cent. of a human erythema dose—the usual "unit dose" used in the therapy of malignant tumors—caused mild acute symptoms of intoxication associated with anorexia, anacidity and hyposecretion. This work confirms the observations of others on the sensitiveness of the intestinal mucosa to roentgen rays, the intestinal mucosa being at least twice as sensitive as the fundal mucosa of the stomach. The findings do not warrant the use of roentgen rays for treatment of conditions in which it is desirable to reduce gastric acidity.

The Influence of Roentgen Rays Upon Progeny. Walther Schmitt,[8] as the result of his study of the literature and his own experience, arrives at the conclusion that thus far no case is known in which, on account of irradiation of the ovary of the mother, deformed or inferior offspring resulted; nor has there thus far been observed later abnormal development of such children. Unfortunately this last question has not been studied sufficiently thoroughly or long for a final opinion. Nevertheless, in the present state of our knowledge, we must consider *temporary Roentgen sterilization justifiable* in view of its well known therapeutic value and lack of proof of later ill effects.

(8) Klin. Wochenschr, July, 1924.

Roentgen Ray Treatment in Whooping-Cough. Henry I. Bowditch[9] presents a discussion of the results of treatment with the roentgen ray in 300 cases of whooping-cough. In our present state of knowledge, the justification for its use seems to be based on the same theory as that for its use in bronchitis—the apparent involvement of the hilum lymph nodes in an acute inflammatory hyperplasia—and the action of the rays on these glands in reducing their sizes. This reduction in size is again more theoretical than actually demonstrable; but the successful clinical application makes the use of the roentgen ray rational. In addition to this action on the bronchial lymph nodes, there is the possible theoretical direct action on the bacteria and on the hematopoietic system in general. Experimental laboratory work along these lines is slowly being carried on.

The clinical course of the disease under treatment [for the technic of which the original paper will have to be consulted] seemed to be modified very definitely. Within a few hours (about eight) after the first treatment the patient experienced a feeling of relief. The symptoms were reduced in severity and duration. At the end of 24 hours the symptoms usually reverted to their former degree, and the next day no very marked effects from the treatment were noted. After the second treatment the symptoms usually fell back a little. There were cases in which the severity of the paroxysms was less than after the first treatment. The most marked changes followed the third treatment. The patient seemed more noticeably relieved, the severity of the paroxysms was reduced, whooping almost disappeared, cyanosis and vomiting became minor factors, and often more uninterrupted sleep at night ensued. By the end of a week the appetite usually improved and the patient was much better. Few patients had more than four treatments. There is strong evidence that over 80 per

(9) Jour. Amer. Med. Ass'n., May 3, 1924.

cent. were benefited by the treatment. Only one fatal case occurred in the entire series. The most favorable results seemed to be obtained in the early stages of the disease and in the younger children.

Spleen Irradiation in the Treatment of Malaria. Ivan I. Manoukhin[1] of the Institute of Experimental Medicine, Petrograd, reports a new treatment of infectious diseases to which he gives the name the "self-defensive reaction." He believes that this method exercises a curative action in widely different infectious diseases such as lobar pneumonia, recurrent typhus, catarrhal pneumonia, tuberculosis, typhoid, dysentery, and tetanus. The treatment of malaria here described is only a particular instance of the application of the method.

The author's experiments showed that leukocytolysis is the basis of this self-defensive reaction. He believes that the premier role in the defensive struggle of the organism against infection and its toxins is that of leukocytolysis and not that of phagocytosis. Phagocytosis never comes into play unless the microbes are greatly weakened and their toxins neutralized by the preceding phenomenon of leukocytolysis.

The self-defensive struggle of the organism against Laveran's parasite merely constitutes a particular instance of the general self-defensive reaction. It explains the characteristics of the leukocytic formula in malaria, which is as follows:

1. Hypoleukocytosis takes place chiefly at the cost of polynuclears, their number falling to 40 and even to 20 per cent. observed at the period of apyrexia.

2. Hyperleukocytosis, also at the expense of polynuclears, begins during the chill and reaches its maximum when the hematozoa spread in the serum in the form of small ameboid bodies in order to infect new corpuscles. According to Billet it reaches 12 to 20 thousand, continues during the whole period of fever,

(1) Lancet, Jan. 26, 1924.

and ceases with the appearance of sweating, being then transformed into hypoleukocytosis always shortly before the fall of the temperature. In that way the general characteristics of the leukocytic curve in malaria are the same as those found in all the cases of self-defence of the organism against infection; that is to say, the curve consists of alternative periods of hypo- and hyperleukocytolysis. The only particular characteristic of the evolution of self-defence against Laveran's parasite is found in the prolongation of the periods of hypoleukocytosis at the cost of the periods of hyperleukocytosis. The lymphocytosis is the result of the massive diminution of the number of polynuclears.

The author has succeeded in showing that the hypoleukocytosis in malaria really takes place exclusively because of massive destruction of leukocytes in the blood. This leukocytolysis is caused by the presence of leukocytolysins, while at the moment of hyperleukocytosis the presence of antileukocytolysins is observed; the substitution of the antileukocytolysins by the leukocytolysins always slightly precedes the beginning of the fall in temperature.

The increased production of leukocytolysins necessary to the leukocytolysis is regularly accompanied in malaria by a marked enlargement of the spleen volume, which undoubtedly shows that the activity of this organ is insufficient for the requirements of the organism as a whole when the latter is attacked by Laveran's parasite. Hence the radical treatment of malaria should realize an artificial activation of the function of the spleen cells, until that function fulfills the needs of the organism with regard to leukocytolysis. With this in view the author used a dose of *x*-rays equal to 1h. (Holzknecht unit) as measured by the Sabouraud and Noiré radiometer. The rays are filtered through 1 mm. of aluminum, and the Holzknecht scale is used. This dose is administered for five minutes at 1 milliampere, with *x*-rays

(hardness, 8 on the Benoist radiochronometer, 15 cm. on the spintometer), with the anticathode at a distance of 25 cm. from the surface of the body.

The antileukocytolysin the author believes to have shown is elaborated by the liver. As, therefore, liver and spleen are antagonistic, great care must be taken that during radiation of the spleen the rays should not reach the liver. Radiation of the spleen should be made either from front or back, but not from the side. The frequency of spleen radiations in acute malaria should be regulated according to the form of disease present. In quotidian fever a radiation should be given every day with interruption for five or seven days if reduction of temperature has not begun after the tenth application. In tertian and quartan fever the radiations should be made on the eve of the attack.

In chronic malaria spleen radiations should be applied every two, three, or five days, according to the facts of the individual case. If one series of fifteen radiations is insufficient for the establishment of a complete cure the patient should be rested for a month and treatment then recommenced, again not exceeding the number of fifteen radiations. In very refractory cases a third series of radiations of the spleen should be given after another month's rest.

From a comparison of results obtained at Kieff by the "self-defensive treatment" and by quinin, in two hospitals (his own and No. 19), he draws the following results: No. 19 hospital, where quinin was used, had deaths to report, whereas his hospital had none. The benign clinical evolution of malaria in the patients submitted to the spleen radiation was striking, their general condition improving after a few applications of the rays. The duration of the disease was shortened on an average to nearly a third of the duration observed with quinin treatment. No. 19 hospital contained some more or less pronounced quinin-resistant forms of malaria; pa-

tients who left his hospital all showed a definitive return to the normal conditions of the blood. Several relapses were observed in quinin cases, even before the patients had left hospitals. The author was fortunate in being able to keep in his hospital all patients who had undergone treatment for at least a month after their recovery. It was also possible to examine patients a year and two years after the end of their treatment. In none could any return of malaria be found or reported. Finally in this "self-defensive treatment" we have a powerful expedient in cases of quinin idiosyncrasy. Comparison of the results of this method with those obtained in the few available cases treated by neo-arsphenamin were still more strikingly in favor of the former.

Roentgen Rays in Tonsillar Infection. W. D. Witherbee[2] claims that fully 80 per cent. of cases observed from one to three years suffering from recurrent attacks of tonsillitis and pharyngitis have been relieved of this condition.

The infection in these cases involves not only the tonsils and the adenoids but extends to the lymph structures on the lateral and posteror walls, the infratonsillar nodule, lingual tonsil, the lymph tissue in the fossa of Rosenmueller and the cervical glands of the neck.

The surgical removal of tonsils and adenoids in delicate children is followed by pharyngitis due to the infection present in the adjacent lymph structures, thus retarding convalescence. The removal of the embedded tonsil necessitates cutting or tearing through the tissue surrounding the tonsil and thus increases the possibility of dissemination of septic amboli into the blood and lymph tissues. On the other hand, the effect of the roentgen rays would cause not only a shrinkage and drainage of the lymph structures involved, but would also produce a local immunity by means of the biochemical change taking place in these tissues. By this

(2) Jour. of Radiology, April, 1924.

means the surgical complications, lung abscess, septicemia, pneumonia, and acute endocarditis may be avoided.

Limitations in the Radiotherapy of Cancer. Francis Carter Wood[3] discusses well the limitations of irradiation therapy in malignant disease and classifies them under four headings: (1) physical, (2) those dependent upon the general sensitiveness of the patient to radiation, (3) upon the anatomical relations of the tumor, and (4) upon the resistance of the tumor to radiation.

1. The physical limitations are obviously those governing the supply of a sufficient amount of energy to the neoplastic structures to be influenced, for there is no evidence that a cure of cancer can be produced except by the destruction of the cells of the neoplasm itself. Unfortunately there is not the slightest evidence that any immunity exists against cancer, nor can immunity to an established tumor be induced by any process with which we are at the present time familiar. The connective tissue sclerosis produced by heavy raying certainly does not destroy the few remaining cancer cells, for recurrences of tumors belonging to the relatively benign basal cell group may be seen following radiation after a period of eight or ten years. If the connective tissue had a destructive action it surely should have been effective in this time.

The setting free of a sufficient amount of energy in accessible tumors is most easily done by the insertion of radium. Whether glass capillaries containing emanations shall be used, or whether the emanations or the radium salts shall be screened by a considerable amount of metal is still a matter of discussion, and the preferable technic can only be settled by prolonged clinical observation of patients treated by both methods.

Thus, radium offers no therapeutic advantage over *x*-ray, except for the fact that it can be inserted into the substance of the tumor and that, owing to the inverse

(3) New York State Jour. of Med., November, 1923.

square law, the general damage to the body is less than when a powerful beam of *x*-ray must be passed directly through healthy structures to reach the tumor.

Deep lesions require a shorter wave-length in order to get a proportionately sufficient dose into the depths. The only question with *x*-ray is to use sufficient voltage to obtain *x*-rays of such a short wave-length that a sufficient dose may be placed in the tissues without excessive skin injury. Otherwise there is no advantage in using high voltage. The practice at present tends, even in Germany, toward the abandonment of the high voltages originally tried, for as good results are evidently obtained with considerably lower electrical pressure and a corresponding prolongation of life of the *x*-ray tube.

2. Certain persons bear radiation badly. Radiation sickness due to tissue destruction which regularly follows heavy treatments usually occurs in neurotic persons of both sexes. There are, however, people who cannot stand even moderate doses applied to the chest, and some who suffer from severe and even dangerous radiation sickness when the lower abdomen and pelvis are radiated. Deep therapy is absolutely impossible in such persons. Cachectic persons, as is well known, bear deep radiation very badly, and, as a rule, should not be treated except very lightly and then only for temporary palliative effects and the psychic benefit that they obtain. Heavy doses may result in the death of the patient within a few weeks with progressive anemia, nausea, and the development of a condition which resembles uremia in some of its clinical aspects, but without the chemical changes in the blood seen in that condition.

3. The third limitation of radiotherapy is the site of the tumor in relation to other important organs of the body. Thus, for example, carcinoma of the stomach or the liver is usually not amenable to deep radiation for the reason that it is almost impossible to avoid injury

to the pancreas, adrenals, and sympathetic system. The damage which occurs in the liver when hepatic or gastric tumors are rayed is often serious; and the patients do not, with rare exceptions, do at all well. The result in carcinoma of the stomach, even with the most careful distribution of the radiation, is so unsatisfactory and the general depression produced is so great that it is usually wiser not to attempt even palliative radiation on this region. In the lower abdomen and pelvic region it is much easier to give heavy doses, some persons being able to stand enormous quantities of *x*-ray without disturbance of their general condition. Radiation of tumors of the scalp, of the brain, of the nose and throat, implies certain difficulties such as the necessary alopecia which inevitably follows sufficient dosage, and danger of coincident damage to the thyroid, pituitary, and salivary glands. It may be stated positively that only palliative results can be obtained. Where radium can be inserted, the palliative results are better, but effective treatment can be carried out only in certain types of tumor. The use of buried radium in lingual and tonsillar cancer has resulted in excellent, and in some rare instances, prolonged palliation, though it is impossible to state at the present time whether these benefits will be permanent. Carcinoma of the lip confined to the mucous membrane can be cured locally by large doses if there is no involvement of the regional nodes. But the practical difficulty is to discover whether these nodes are invaded or not, so that some operators believe in excising these nodes while treating the lip by means of radiation. It is a far wiser procedure to excise both the lip and the nodes, because statistical observations have not been able to show, for radium or *x*-ray, as satisfactory results as have been obtained by surgery.

All tumors of the extremities can be rayed with full dosage and beneficial palliative results obtained if the tumors are radio-sensitive. Serious constitutional symptoms do not appear after such treatment, but the local change is apt to be great.

4. The fourth limitation of radiotherapy lies in the biology of the tumor. Tumors, even if they are of the same morphology, vary greatly in their resistance to radiation. But few general rules can be drawn in regard to the radio-sensitiveness of human tumors. One is, of course, the well-known phenomenon that the basal cell tumors of the skin are radio-sensitive; and if they do not contain squamous cells, can be cured by proper use of radiation methods in 90 per cent. if taken before the tumor has reached a considerable size. If, however, bone or cartilage is invaded, the tumor becomes much more resistant and the final result doubtful. Also, tumors which have been treated by caustics, solid carbon dioxid, or previous radiation, are much more difficult, and in many cases do not yield at all. The lymphosarcomata also are often radio-sensitive, but not always.

The only other generalization possible with human tumors is that those which are highly vascularized and rapidly growing very often yield temporarily, at least, very astonishing clinical results. The apparent cure is, however, by no means permanent. The reason for this is that one of the primary effects of radiation is upon the capillaries, causing thickening of the endothelium, perivascular edema and infiltration, and ultimate thrombosis of the vessels. This obviously results in extensive necrosis in the central portion of the tumor with secondary necroses following upon the destruction of the cells, their softening and absorption. The process, however, soon comes to a limit, and leaves, as a rule, a shell of tumor still perfectly vascularized from the larger arterioles coming directly from the normal tissues

which surround the tumor. The failure, up to the present, in obtaining satisfactory results means that the tumor cells thoroughly supplied with circulating blood through capillaries or arterioles which cannot be thrombosed by radiation approach very closely to the limits of resistance of the normal tissue. In our efforts to destroy the last few cancer cells which may remain, the normal cells must receive serious damage, even to such a degree as to jeopardize or destroy the life of the patient. For example, in endeavoring to destroy carcinoma of the cervix uteri, a number of examples of perforation of the intestine have been seen. If the vascular tumors are sensitive, then it is a safe conclusion that the tumors which have little vascularization are insensitive. This is also roughly true. The fibrosarcomata, the osteochondrosarcomata, and the osteoidsarcomata, or the ordinary simple, benign fibromata with little but supporting tissue, are markedly radiation-resistant.

The widely heralded carcinoma and sarcoma dose suggested by Seitz and Wintz is being rapidly abandoned as meaning anything but the minimum quantity of radiation which will cause temporary recession of a tumor. Of course, temporary recession is by no means synonymous with cure. The Seitz and Wintz dose represents, in all probability, approximately the maximum dose which the tissues will stand without serious injury to the patient, and therefore points to the limitations of our present radiotherapy.

Until more is known of the radio-sensitiveness of human tumors, all radiotherapy is merely empirical and recourse should therefore be had to surgery in all operable malignant tumors, for surgery removes the tumor whether it is radio-resistant or not, its success depending entirely on the extent of the anatomical distribution of the tumor material and not upon any quality of the individual cells.

If surgery should be used on all operable malignant growths it is equally true that those which are inoperable should be treated by radiation. Meddlesome and partial surgery is worse than useless and only brings discredit to a method which has achieved so much.

In the palliation of inoperable neoplasms and postoperative prophylactic raying lies the present field of radiation, and the results are often so good that we may look forward with confidence to greater achievements in this direction in the future.

The present status of roentgenotherapy of carcinoma, most especially of the uterus, is also discussed by Fritz Heimann[4], who arrives at the conclusion that, with an absolute cure in 9.3 per cent. of cases and a relative cure in 45.5 per cent., *operation offers better prospects than even the most energetic modern deep therapy* with absolute cure in only 4.3 per cent. and a relative cure in 16.6 per cent. of cases. The general result of irradiation is an immediate improvement which continues for longer or shorter time until the remaining carcinoma cells have again obtained the upper hand and the cancer takes on renewed growth. Nevertheless *the rays are the best palliative we have in the treatment of inoperable carcinoma.*

The further improvement in technic will obviously not be in the direction of still greater dosage, for the dosage now used is as great as the organism can tolerate. Indeed, there is a possibility that we may see a return to more moderate dosage, as the suspicion is justified that extreme dosages damage the system to such an extent as to impair its resistive power. The fear that smaller dosage may have a stimulating effect is not justified, according to Holzknecht, who points out that no one has demonstrated such an action. Holzknecht, indeed, doubts whether the examples usually cited for stimulation by roentgen rays could not be explained by their well-known destructive action. Thus, the irra-

(4) Klin. Wochenschr, Aug. 5, 1924.

diation of the spleen in hemorrhage depends for its therapeutic action upon destruction of lymphocytes and the consequent increased formation of fibrin ferment. The diuretic effect of irradiation in nephritis may also be due to destruction of leukocytes, thus obtaining relief of tension such as may also be produced by decapsulation. The apparent stimulation of the ovary resulting from roentgenization in amenorrhea would be explained by Holzknecht quite as well by a removal of inhibition.

Prophylactic irradiation after operation gives, at least as far as the uterus is concerned, excellent results.

ROENTGENOGRAPHY

Roentgenography of the Gall-Bladder. To visualize the gall-bladder, E. A. Graham, W. H. Cole and G. H. Copher[5] inject intravenously a solution of 5 or 5.5 gm. of the crystalline sodium salt of tetrabromphenolphthalein heated in 40 c.c. of distilled water, and sterilized in a boiling water bath for fifteen or twenty minutes. The solution is given preferably in two doses, great care being taken not to allow extravasation of the solution outside the vein on account of the danger of necrosis.

The following orders are given to the patient: omit breakfast and lunch; take 2.6 gm. of sodium bicarbonate every three hours for 48 hours day and night while awake; lie on right side of the abdomen or be up; take water, if desired, by mouth; and to omit protein from the evening meal on the day of injection.

Roentgen ray films are taken at four, eight, 24 and 32-hour periods.

A normal gall-bladder will begin to cast a shadow from three and one-half to five hours after the injection; will show a tendency to change in size; will cast its heaviest shadow between 16 and 24 hours, and empty

(5) Jour. Amer. Med. Ass'n., May 31, 1924.

in about 48 hours. The shadow shown on the four or eight-hour plate is almost invariably larger than the subsequent shadows. So far, all gall-bladders that failed to show this "elasticity or distensibility" at some time during the series when the injection was followed by the routine given above have been found to be pathologic at operation, or to give definte clinical findings of gall-bladder disease. Pathologic gall-bladders do not cast so heavy a shadow as normal ones, since the production of the shadow is dependent on the concentration power which may be partially or completely destroyed by disease. In four cases in which the routine order was followed, the gall-bladder failed to cast a shadow. All of these patient were operated on. Two had a stone occluding the cystic duct; one had a gall-bladder so scarred and contracted by disease that it was too small to cast a shadow.

In all patients with cholelithiasis in which the cystic duct was not occluded, the stones have appeared as either negative or positive shadows, but only after the injection of the dye.

Roentgenography of Spinal Canal (Myelography). French surgeons, notably J. A. Sicard, P. Paraf and L. Laplane[6] have reported several instances of the use of iodized oil (Lipiodol 1 to 2 c.c.) in conjunction with the roentgen ray for the localization of spinal and cranial lesions. E. C. Russell[7] reports an additional case in which roentgenography, after introduction of 2 c.c. of iodized oil into the cisterna magna, helped to localize a spinal tumor. The iodized oil, being heavier than the spinal fluid, seeks the level and in cases without obstruction will be found at the lowest point. In this case, the impervious material was seen opposite the body of the fifth dorsal vertebra. Laminectomy was performed, and a tumor removed at the level indicated.

(6) Presse Méd., Oct. 24, 1923.
(7) Jour. Amer. Med. Ass'n., May 31, 1924.

H. Peiper and Heinrich Klose[8] have employed an especially prepared iodized oil (Iodipin) for this purpose, and arrive at the conclusion that, while the method is of promise, it should be confined to the hands of the expert, and its indications limited as much as possible.

Intra-Arterial Injection of Sodium Iodid. Barney Brooks[9] describes the following technic for determination in the living patient of the amount and extent of occlusion of the arteries of the extremities.

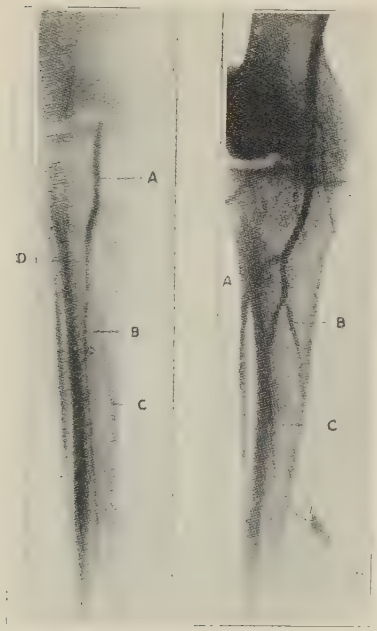
The solution injected is prepared by dissolving 100 gm. of sodium iodid crystals in 100 c.c. of distilled water. The solution is sterilized in the autoclave and is always used soon after its preparation. The solution should be colorless or very faintly yellowish. A solution that shows any considerable iodin color should not be used.

The method of obtaining the roentgenograms of the arteries of the lower extremities is as follows:

The entire thigh is prepared for operation. A sterile tourniquet is placed around the thigh as high as possible, but is not tightened. With a local anesthesia by 0.5 per cent. procain the femoral artery is exposed in the proximal end of Hunter's canal. Only enough of the artery is exposed to permit the application of a Crile artery clamp, which is not tightened. The roentgenray tube is placed over the knee region and a large photographic film with a screen is placed under the knee and leg. The patient is now given nitrous oxid gas. It has been found that there is pain during the period the solution is in the artery and the patient cannot be kept still enough to get a good roentgenogram unless a general anesthetic is used. The tourniquet proximal to the exposed artery is tightened enough to produce a filling of the veins. When the veins are full, the clamp on the artery is tightened enough to occlude the artery completely. A short interval is then allowed

(8) Klin. Wochenschr, Dec. 2, 1924.
(9) Jour. Am. Med. Ass'n., Mar. 29, 1923.

PLATE II.



a *b*

a—Appearance after intra-arterial injection of sodium iodid. The popliteal (A), peroneal (B) and posterior tibial (C) arteries are injected; there is no injection of the anterior tibial artery; a faint outline of the origin of this vessel can be seen (D). This injection was done without a general anesthetic, and the sharp outlines of the injected vessels are obscured by movement.

b—Appearance after intra-arterial injection of sodium iodid. The popliteal artery shows no obstruction; the anterior (A) and posterior (B) tibial arteries are injected for only a short distance; the origin of the posterior tibial artery is markedly constricted; the lumen of the peroneal artery (C) shows marked irregularities.—Brooks, page 358.

to elapse for the artery distal to the clamp to empty its blood. A medium sized needle is introduced into the lumen of the artery and 10 c.c. of the sodium iodid solution is injected. The roentgen ray tube is then operated for the briefest period possible to secure a good plate. A second plate may be taken of the distal third of the leg and foot. The tourniquet is released, the clamp removed from the artery, and the gas anesthetic discontinued. The wound is then closed.

This method has been found to give valuable information as to the location and extent of arterial obstruction. It has also, in several instances, established the fact that conditions presumed to be due to arterial obstruction had other causes. In those instances in which the method has been used there has been no manifestation of injury to the artery from the injection. (Plate II.)

J. Berberich and S. Hirsch[1] have successfully employed, for the same purpose, intra-arterial and intravenous injections of 5 to 10 c.c. of 10 to 20 per cent. strontium bromid solution.

Mercuric Iodid in Pyelographic Medium. John H. Cunningham, Roger C. Graves, and Tenney L. Davis[2] point out that sodium iodid, though the best available pyelographic medium, lacks one important quality—that of germicidal activity. They have decided after consideration of all possible antiseptics in connection with a pyelographic solution, that the addition of 1:3,000 mercuric iodid to 12 per cent. sodium iodid is the most satisfactory. Such solution added to an equal amount of a colon bacillus infected urine, destroyed bacterial growth in two and one-half minutes. The solution retained in the mouth for a considerable period produces a salty taste but no irritation of the buccal mucosa. Introduced into the circulation of a rabbit, it produced no significant change in the condition of the animal so far as heart, blood pressure, and respiration were con-

(1) Klin. Wochenschr, Dec. 3, 1923.
(2) Jour. Urology, September, 1923.

cerned. This solution is employed routinely in the authors' clinic and thus far they have observed no immediate or subsequent ill effects or discomfort following its use in either the bladder or renal pelvis, even in the presence of active inflammation. This solution reduces to a minimum the risk of introducing infection; and it provides some degree of positive benefit, apart from diagnosis, in cases in which infection already exists. The solution is prepared by dissolving 1 gram of mercuric iodid in 3,000 c.c. of 12 per cent. sodium iodid. The latter is made with chemically pure sodium iodid and distilled water. The final solution does not need to be boiled.

ACTINOTHERAPY

Mercury Vapor Quartz Lamp in Rickets. Edwin T. Wyman and Charles A. Weymuller[3] report that all of 86 cases of acute rickets treated with ultraviolet irradiation showed steady improvement. The patients were exposed to the "Alpine sun" lamp at a uniform distance of 20 inches from the surface of the body. The initial treatment was two minutes to the front and two minutes to the back of the body, a total of four minutes. This exposure was increased one minute to the front and one minute to the back, a total of two minutes, each successive treatment until an exposure of fifteen minutes to the back and fifteen minutes to the front, a total of thirty minutes, was given. This routine could be carried out without undue erythema with even the most delicate skins. None of these patients received cod liver oil or other medication, and the diet was not interfered with. The authors conclude that acute rickets can be cured in an outpatient department by ultraviolet irradiation, the treatments being given three times a week without any other antirachitic medication, though they admit

(3) Jour. Amer. Med. Ass'n., Nov. 8, 1924.

that ultraviolet irradiation in combination with cod liver oil probably hastens the healing processes more than either ultraviolet rays or cod liver oil alone. They also believe that ultraviolet irradiation three times a week prevents the development of rickets. If the progress recently made in manufacturing fused quartz continues, it may soon be possible to have quartz windows in every nursery so that the baby can have its daily sun bath in a warm room. It may also be possible to devise an electric quartz bulb, simple to operate, harmless and inexpensive, which will give off sufficient actinic rays, with from one-half to one hour exposure a day, to prevent the occurrence of rickets in babies.

HELIOTHERAPY

Heliotherapy. E. J. Melville,[4] after a four years' sojourn in St. Petersburg, Fla., the so-called "Sunshine City," feels qualified to speak with some authority upon the above subject of sunshine. St. Petersburg had, last winter, 25,000 invalids suffering from some painful internal affection, cardiovascular conditions, asthma, and bronchitis. That many of these had obtained relief and remained as permanent inhabitants is proved by the fact that the city doubles its population nearly every year.

This city is claimed to have a greater number of sunshine hours than any other spot in the civilized world. The temperature in this American Riviera for eight months of the year hovers around 80°, with a drop during January and February of about 15° and a rise of 10° in August and July. During the season, from November until May, there is no rain. In June, July, and August it rains every day and sometimes several times a day, but so evanescent are the showers and so

(4) Amer. Med., May, 1924.

porous the sandy soil that little trace of moisture shows half an hour after a downpour except in promoting the marvelous growth of a tropical garden.

In spite of the fact that many workers remain exposed to the sun here all day when the thermometer hovers around 90°, the author has yet to see a case of heat stroke or sun stroke. The air being so dry, the worker perspires profusely and this produces a cooling of the body due to the latent heat of evaporation. Furthermore, St. Petersburg, situated on the tip of Pinellas Peninsula, gets the benefit of ocean breezes from three sides.

The writer, seeing the remarkable improvement in patients who loafed on the beaches in bathing suits, had constructed in his yard a small solarium where the patients might lie naked on a clean, comfortable cot and take the sun cure on the whole body. Four uprights to which are attached blankets or other screening, and a cot upon which to recline makes as good a solarium as any if one has a roof or back yard at his disposal. The treatment is begun with short exposures twice a day of ten minutes' duration, with protection of the eyes and head. The length of exposure is gradually increased until the patient is thoroughly tanned. Then he may remain in the sun practically all day. One must avoid chilling or blistering as this discourages the patient. The patient may get an overdose of the sun without being blistered or even reddened. The symptoms in such a case are those of acute protein poisoning —headache, vomiting, fever, nausea, and general malaise. Though in chronic cases one may get psychic improvement immediately, as one will upon the exhibition of anything new; the real curative effects do not come into play until the skin is well pigmented by exposure.

Though sunshine has been known as a therapeutic agent since the days of the early Egyptians, it was not until recent years that it was found that children with

rickets who were fortunate enough to be placed in the bed exposed to the sun improved more rapidly than those dosed with codliver oil.

The author concludes with the following practical observations. Sunlight, *per se,* is not an antiseptic. The beneficial results are derived in skin diseases from the hyperemia induced. The sun bath is of great value in anemia and all atonic conditions. The sun will "pep up," or recharge, the human battery run down from any cause. All convalescents gain more rapidly when exposed to the air and sun under intelligent supervision. All painful affections of the chronic type are benefitted as the surface of the body becomes reddened under the sun treatment, which means that the deep structures are correspondingly depleted. Pressure is thereby lessened, and we know that pressure always means pain.

Disabuse your patient's mind from the bugaboo "taking cold." You will get your most brilliant results in winter, even in northern winters. See what Rollier is doing in the mountains of Switzerland in winter; 99 per cent. of infections of the upper air passages commonly called "colds" might more appropriately be called "heats," as undoubtedly they are caused by too much coddling

CLIMATOTHERAPY

Climato-physiology. A. Loewy[5] discusses some newer developments in this rather new study; for though the therapeutic use of climate dates from remotest antiquity the scientific study of its effect is hardly older than half a century. The author devotes the present article most especially to the effect of radiant energy. This differs in accordance with difference in wave lengths. *The luminous rays increase most especially the desire*

(5) Klin. Wochenschr, June 3, 1924.

to move. Individuals exposed to light become more energetic and this leads to an increase in metabolism. Even among the luminous rays a difference can be recognized among the different wave lengths. The shortest waves, such as the violet, are the least exciting, the yellow and the green rays, which are the most luminous, are the most exciting. The point of attack of these rays is not necessarily the retina of the eye, because the same results have been obtained upon blinded frogs and eyeless earthworms.

Growth goes on more rapidly in the light than in the dark. This is shown by increased rapidity of development of frog's eggs and larvae, as well as increased rate of growth of limbs of amphibean reptiles in the presence of light. Red blood corpuscles also multiply faster under the influence of light. Rats made sufficiently anemic succumb in the dark, while they recover under the influence of light. The necessity of proper spacing of the stimulus is shown by the fact that, in mice made anemic, an interval of four to five days was required between irradiations, otherwise the anemia became progressive. In excessively irradiated young rats growth was delayed by as much as 50 per cent, as compared with controls. These last named effects are chiefly inherent in the violet rays.

The question is how the rays affecting the body surface become active in the interior of the organism. Direct experiments have shown that light rays are capable of increasing fermentative processes in the animal tissue. Thus it has been shown that there is increased energy of oxidation in tissues or blood exposed to light as compared with darkness. This can be made visible by injection of methylene blue. Parts of the skin made blue by such injection and exposed to light lose their color much quicker than those kept dark. Evidently the methylene blue is remarkably reduced in the parts exposed. That such an effect may also extend into the depths is to be anticipated from the fact that blood is

photo-active and that this photo-activity can be greatly increased by exposure to light. This, in turn, seems to be connected with increased oxidation processes. The ferments, also, that deal with intermediary metabolism are influenced by light. Irradiated animals are capable of destroying nucleic acid and its derivatives, such as uric acid, etc., much more completely than those not irradiated. It has been shown that the uric acid elimination in man is also diminished, evidently because it is more completely metabolized. Protease and lipase as well as the sugar splitting ferments are likewise rendered more active. Repeated irradiations of diabetics have many times produced a decrease of blood and urinary sugar, and in some cases a marked lessening of acetone bodies.

It has been shown that all these effects of light upon ferments are much more prominent after small injections of eosin or other fluorescence producing dyes, which seem to sensitize the tissues to light rays. Such sensitization may also be produced by the billary pigment.

The skin absorbs as much as 90 per cent. (in the negro 95 per cent.) of the radiant energy to which it is exposed, most especially the short wave lengths, while the red and ultra red rays penetrate deeper and are capable of affecting the capillary net work of the skin and, through it, the rest of the body. The absorbed light rays are not lost, however, for radiant energy affects only those objects by which it is absorbed. The most obvious result of this is the occurrence of pigmentation. This develops, probably exclusively, in the basal cell layers of the epidermis from one, or possibly more, chromogenic precursors. These are products of protein metabolism wherein most especially the aromatic amino-acids are involved—in the first place dioxyphenylalanin, a compound similar to tyrosin. It is believed that the basal cells of the skin have a certain attraction for these

amino-acids and that they, with the aid of a specific ferment contained in them, produce increased conversion into melanin under the influences of the rays.

From the irradiated skin cell destruction products, formed, like the melanin, in increased amounts, also enter the interior of the body. It is these substances in the blood of animals exposed to light that are liable to produce fever after prolonged exposure. We evidently have here a process similar to that long known to occur as the result of extensive burns of the skin, for which, likewise, abnormal tissue destruction products are considered responsible. That substances enter the circulation from the skin we are forced to conclude from observations that tuberculosis localizations not directly exposed to light were influenced by treatment of other portions, even of healthy skin.

The formation of antibodies is likewise strongly influenced by light rays. Thus, it has been shown that precipitation, hemolysis, and anaphylactic reactions are affected; and, in accordance with observations at present available affected in the direction of a diminution, even abolition, of action. These observations furnish a beginning for the understanding of the effect of light upon infectious diseases.

Mountain Climate Helpful in Lowland Asthma. W. Storm van Leeuwen, H. Varekamp, and L. Bien[6] conclude, as the result of a clinical study, that asthma is in most cases, due to inhalation of some colloidal substances which, in the great majority of cases, seem to be undeterminable. In a special study of three Hollanders suffering from asthma it was found that elevation of about 1,000 feet showed some improvement which became marked at 2,400 feet. Nearly all asthmatics were free from attacks at elevation between 4,000 and 5,000 feet. Sojourn in mountain climate does not, however, cure the tendency to asthma, and, to permit the

(6) Klin. Wochenschr., Mar. 25, 1924.

patient to return to the lowlands, it is necessary to treat him anti-allergically to desensitize him. For this purpose the asthmogenic substance might be used. When not available tuberculin may be employed with advantage. The technic of the tuberculin treatment of asthma has been discussed by the authors in *Münch med. Wochensch.*, p. 849, 1922.

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